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THE NEPHROPATHY OF POTASSIUM DEPLETION*

A Clinical and Pathological Entity

ARNOLD S. RELMAN, M.D.,† AND WILLIAM B. SCHWARTZ, M.D.‡

BOSTON

IT is the purpose of this report to describe the clinical and functional aspects of the renal disease associated with potassium depletion in man, and to correlate these with the histologic changes found in renal tissue obtained by serial biopsies.

It is well known that experimental depletion of potassium produces renal tubular lesions in rats.[1-3] Although there have been a few recent reports of renal lesions in human subjects dying with potassium deficiency,[4-7] the clinical and physiologic implications of the renal damage have not received attention until recently. A previous report[8] described 2 patients in whom marked but apparently reversible disturbances in tubular and glomerular function had developed in association with severe potassium depletion. Serial observations of renal function have now been carried out in a total of 5 potassium-depleted patients who had evidence of renal disease, and in 3 of them kidney biopsies were obtained. These data, considered together with other autopsy material and the existing reports in the literature, strongly suggest that the nephropathy of potassium depletion is a distinct entity that is not uncommonly encountered in a great variety of clinical situations.

CASE REPORTS

CASE 1. F.C., a 45-year-old man, had suffered from diarrhea since the age of 20. Repeated investigations had failed to provide any specific diagnosis, but since there was excessive fecal loss of nitrogen and fat, without any other indication of sprue, it was considered that he had some type of chronic malabsorption syndrome. He had noted marked polyuria and polydipsia for several years. After a particularly acute episode of diarrhea severe muscle stiffness and weakness had developed and a serum potassium of "below 2.0 milliequiv. per liter" was found at another hospital. After receiving an unrecorded quantity of potassium chloride parenterally for a few days he was referred for study.

Physical examination showed an emaciated and weak man who had no neuromuscular disturbances except for definite myotonia. A blood count and urinalysis were not remarkable, but the specific gravity of the urine was never above 1.010. Urinary volume was 5-6 liters a day. The serum potassium was 3.1 milliequiv., the sodium 145 milliequiv., and the calcium 3.7 milliequiv. per liter. The serum albumin was 3.3 gm. and the blood nonprotein nitrogen 31 mg. per 100 ml. Renal-function studies were first carried out 2 weeks after admission, when the serum potassium had increased to levels of 3.6-3.9 milliequiv. per liter as the result of administration of oral supplements of potassium. Endogenous creatinine clearance was 86 ml., inulin clearance 64 ml., and para-aminohippuric acid 247 ml. per minute.§ The maximum specific gravity of the urine, with vasopressin (Pitressin) stimulation, was 1.005, and 12 per cent of injected phenolsulfonphthalein dye appeared in the bladder after 15 minutes.

Open biopsy of the right kidney was carried out at this time, and examination of the specimen of renal cortex revealed a striking and diffuse degenerative change in the tubular epithelium (Fig. 1*A* and *B*).

During the next year the diarrhea persisted, and despite attempts to replace stool losses of potassium by oral supplements of potassium chloride, serum potassium remained moderately low. The serum carbon dioxide content varied between 21 and 25 milliequiv. per liter. On 1 occasion, after the patient had failed to take potassium chloride for several weeks, the serum potassium dropped to 2.9 milliequiv. per liter. At this time excretion of potassium in the urine was only 8 milliequiv. per day. A 2d renal biopsy was carried out approximately 1 year after the 1st, at a time when the serum potassium was between 3.5 and 3.8 milliequiv., and the serum magnesium 0.7 milliequiv. per liter. There had been very little change in renal function. Inulin clearance was 58 ml., creatinine clearance 65 ml., and para-aminohippuric acid clearance 233 ml. per minute. The maximum specific gravity, with vasopressin stimulation, was 1.011, and the excretion of phenolsulfonphthalein was still only 16 per cent in 15 minutes. The 2d biopsy specimen is shown in Fig. 2. Although in some places tubular epithelium looked less abnormal than before, there were still many areas of tubular degeneration similar to that seen in the 1st biopsy. In some tubules clear, discrete vacuoles were seen for the 1st time.

During the succeeding 6 months, the diarrhea was gradually brought under control with small doses of ACTH. With continued administration of potassium the serum potassium concentration rose to normal levels and was kept normal for several months. Polyuria and polydipsia gradually disappeared. Myotonia was no longer demonstrable. All renal functions measured at this time were much im-

*From the departments of Medicine, Boston University School of Medicine and Tufts University School of Medicine, the Evans Memorial, Massachusetts Memorial Hospitals, and the New England Center Hospital.

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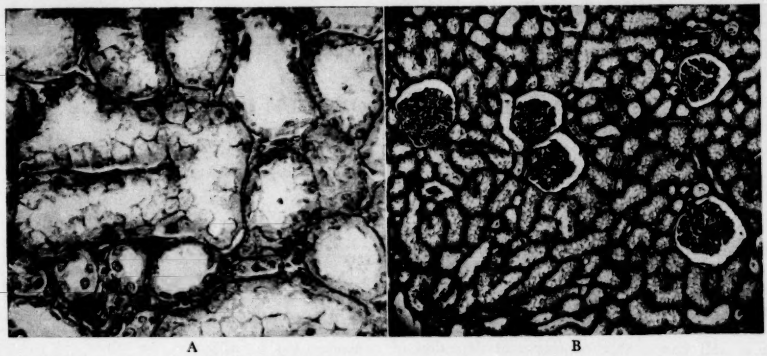
†Associate professor of medicine, Boston University School of Medicine; associate member, Evans Memorial, and visiting physician, Massachusetts Memorial Hospitals.

‡Associate professor of medicine, Tufts University School of Medicine; physician, New England Center Hospital.

§All clearances reported in this study were corrected to 1.73 square meters of body-surface area.

proved. The serum magnesium was now normal. Creatinine clearance was 100 ml. per minute. The maximum specific gravity, with vasopressin stimulation, was 1.022. Phenolsulfonphthalein excretion was 26 per cent in 15 minutes. A 3d and final renal biopsy, carried out at this time (Fig. 3), showed normal tubular epithelium.



A B

FIGURE 1. *Biopsy of the Kidney in Case 1, Showing the Initial Biopsy, at the Height of Potassium Depletion — High-Power* (A) *and Low-Power Magnification* (B) *of the Cortex.*

There is marked swelling of the proximal tubular epithelium, with diffuse "foamy" degeneration of cytoplasm. The glomeruli are normal.

CASE 2.* A.B., a 42-year-old woman, had been taking laxatives containing phenolphthalein and aloin for several years and had slowly lost about ⅓ of her total body potassium. Her chief complaints were vague malaise, weakness and abdominal discomfort. For several months she had noted that her ankles were swollen intermittently.

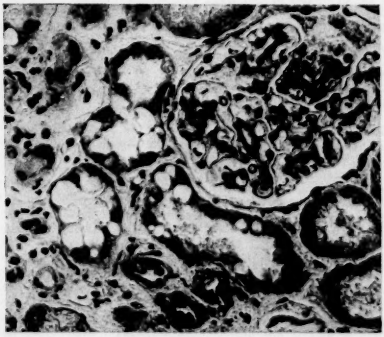


FIGURE 2. *Second Kidney Biopsy in Case 1 after Partial Repair of Potassium Deficit, Showing Diffuse "Foamy" Degeneration to Be Less Marked, with Many Normal-Looking Epithelial Cells.*

Note, however, the appearance of numerous large, discrete vacuoles. These did not stain for fat or glycogen.

Physical examination revealed no abnormality. There were no signs of dehydration, and neuromuscular function appeared normal. The serum potassium ranged from 1.6 to 2.3 milliequiv. per liter. The serum chloride concentration was 94 milliequiv. per liter but the serum sodium, carbon dioxide content, albumin, globulin, cholesterol, calcium, phosphorus and blood sugar were normal. The blood urea nitrogen was 13 mg. per 100 ml. A routine blood count was normal, but urinalysis on admission showed a + test for albumin, with a normal sediment. The maximum specific gravity of the urine after 18 hours of dehydration was 1.005. Urinary potassium excretion was 9 milliequiv. per 24 hours. A barium-enema examination disclosed a moderately atonic, redundant colon, but sigmoidoscopic examination gave no evidence of disease.

Table 1 summarizes the serial studies of renal function during this admission. It can be seen that initially all tubular and glomerular functions were greatly impaired. Immediately after restoration of the potassium deficit (approximately 500 milliequiv. of potassium retained) all functions had improved significantly, although they were not yet normal. Tubular extraction of para-aminohippuric acid was abnormal, indicating that true plasma flow was considerably higher than the plasma flow estimated by para-aminohippuric acid clearance. Six weeks later, with serum potassium and potassium balance continuously normal during the interval, all renal function was normal. The maximum specific gravity was now 1.025.

The patient was not seen for 3 years, after which she returned to the hospital complaining of diarrhea and a fecal discharge from the vagina. She had apparently resumed her habit of laxative ingestion, but x-ray examination of the colon was now diagnostic of ulcerative colitis. The serum potassium had dropped to 2.3 milliequiv. per liter. Urinalysis disclosed a persistent + test for albumin, with 5-10 red cells, 1-2 white cells and 3-6 granular casts per high-power field in the sediment. The clinical tests of renal function are summarized in the lower half of Table 1.

Initially, tubular and glomerular function was grossly abnormal, and injection of vasopressin failed to increase the specific gravity of the urine. Kidney biopsy (Fig. 4) revealed diffuse atrophy and degeneration of the tubules. In addition there were some pyelonephritic scars. With control of the diarrhea and daily administration of potassium, the deficit was gradually replaced, and simultaneously renal function appeared to improve. At the end of 3 months, urinalysis revealed a rare granular cast, but the albuminuria and the red and white cells had disappeared. All clinical tests of tubular function were normal; urea clearance was still below normal although much improved.

CASE 3. L.M., a 25-year-old single woman, was admitted to the hospital complaining of a weight loss of 13.6 kg. (30 pounds), weakness, loss of appetite and muscular

*Reported in detail elsewhere.[5]

aching over a period of 1-2 years. For 2 years she had been in the habit of taking approximately 20 doses of laxatives a day. These laxatives contained cascara, aloin and phenolphthalein, and their ingestion was regularly followed by 4 to 12 watery stools daily. Physical examination revealed a poorly nourished, thin woman without other significant abnormalities. The blood pressure was 88/46. Routine hematologic study was negative, as was urinalysis. The serum potassium concentration was 2.6 milliequiv., the sodium 132 milliequiv., the chloride 96 milliequiv., and the carbon dioxide content 27 milliequiv. per liter. The serum albumin, globulin, calcium and phosphorus were within normal limits. The blood urea nitrogen was 15 mg. per 100 ml. The urinary potassium excretion ranged between 2 and 10 milliequiv. per 24 hours. An intravenous pyelogram showed slight blunting of the calyxes. Urine culture was negative. Renal-function tests disclosed glomerular and tubular impairment. Inulin clearance was 51 ml., endogenous creatinine clearance 70 ml., and para-aminohippuric acid clearance 362 ml. per minute. Urea clearance was 20 per cent normal. The maximum specific gravity, after vasopressin stimulation, was 1.011, and only 9 per cent of injected phenolsulfonphthalein appeared in the bladder in 15 minutes.

Open biopsy of the right kidney was then carried out, and the specimen is shown in Figure 5. There was a diffuse, severe degenerative change in the tubular epithelium, as well as scattered areas of old pyelonephritic scarring.

During the next 3 months, the patient reduced her intake of laxatives to 8 or 10 doses daily and was instructed to take a daily oral supplement of 60 to 80 milliequiv. of potassium chloride. She continued to have several liquid stools each day, and the serum potassium fluctuated between 3.5 and 4.5 milliequiv. per liter. At the end of this time she was readmitted to the hospital for study. The serum potassium was 3.6 milliequiv. per liter, and daily urinary excretion of potassium was 65 milliequiv. Studies of renal function revealed no significant change in glomerular function, but tubular function was now virtually normal. Inulin clearance was 63 ml., creatinine clearance 73 ml., and para-aminohippuric acid clearance 307 ml. per minute. Urea clearance was still only 35 per cent of normal. On the other hand, the maximum specific gravity, with vasopressin stimulation, was now 1.020, and phenolsulfonphthalein excretion was 24 per cent in 15 minutes.

A 2d biopsy of the kidney, done with the percutaneous needle technic, revealed normal tubular epithelium (Fig. 6). Areas of old pyelonephritic scarring were still in evidence.

CASE 4.* R.S., a 24-year-old woman, had become depleted of approximately ⅓ of her total body potassium as the result of chronic overuse of a cascara and aloin laxative compound over a period of several years. She complained of vague muscle pains and weakness, and she had noted nocturia and urinary frequency for some time. For more than 1 year she had observed a tendency to gain weight and for ankle edema to develop whenever she ate salt.

On physical examination there was no evidence of dehydration or of any neuromuscular disorder. Repeated determinations of serum potassium concentrations gave values between 2.1 and 2.3 milliequiv. per liter. Serum bicarbonate concentrations were 30 to 33.5 milliequiv. per liter, but the serum sodium, chloride, albumin, globulin, cholesterol, calcium, phosphorus and blood sugar were normal. The blood urea nitrogen was 16 mg. per 100 ml. A routine blood count was normal, but several urinalyses revealed intermittent + tests for albumin, and a few hyaline casts were occasionally observed in the sediment. The maximum specific gravity of the urine after 18 hours of dehydration was 1.013. The urinary potassium excretion was 3 milliequiv. per 24 hours.

Detailed renal-function studies were not carried out until just after the potassium deficit had been completely restored. Cumulative retention of potassium was approximately 500 milliequiv.; the serum potassium level was 4.5 milliequiv. per liter. The maximum specific gravity was still only 1.013. Inulin clearance was 103 ml., endogenous creatinine clearance 88 ml., and para-aminohippuric acid clearance 379 ml. per minute, and the maximal tubular secretion of para-aminohippuric acid was 74 mg. per minute. Three months later, with potassium balance continuously normal in the interval, the following data were obtained: the maximum specific gravity was 1.026, and inulin clearance was 116 ml., creatinine clearance 133 ml., and para-aminohippuric acid clearance 507 ml. per minute, and the maximal secretion of para-aminohippuric acid 93 mg. per minute. Thus, although partial improvement in renal function had probably already occurred at the time of the 1st detailed measurements, the final values were all definitely higher and within normal limits. In retrospect, therefore, it seems evident that renal function had been significantly impaired during the deficiency state.

*Reported in detail elsewhere.[9]

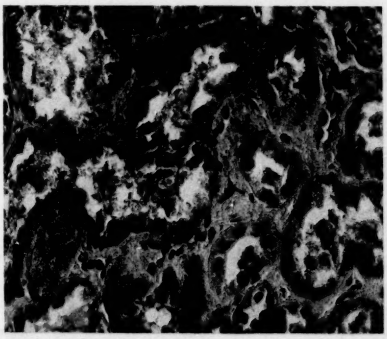


FIGURE 3. *Final Kidney Biopsy in Case 1, after Complete Restoration of the Potassium Deficit (High-Power Magnification of the Tubules in the Cortex), Showing Complete Restoration of Normal Cellular Architecture.*

CASE 5. S.T., a 60-year-old man with the sprue syndrome, was admitted to the hospital complaining of weakness after many weeks of particularly severe diarrhea, which had developed despite treatment with cortisone (25 mg. per day) and folic acid. Physical examination disclosed emaciation, marked generalized muscle weakness and hyporeflexia. A routine blood count was normal. The urine gave a + test for albumin, and the spun sediment contained a rare hyaline and granular cast. Culture of the urine was negative. The serum potassium concentration was 1.7 milliequiv. per liter. The serum sodium, chloride, carbon dioxide content and phosphorus were normal. The serum albumin was 2.8 gm., the globulin 3.4 gm., and the calcium 2.8 mg. per 100 ml., and the alkaline phosphatase 6.7 Bodansky units. The blood nonprotein nitrogen was 45 mg. per 100 ml.

The renal-function studies performed before and after correction of the potassium deficit are summarized in Table 2. Before treatment all tubular and glomerular functions were greatly depressed. A month later, after daily intravenous administration of potassium chloride had restored serum potassium and potassium balance to normal, there was considerable improvement. The final opportunity to measure renal function occurred approximately 2 months after therapy had begun, when urinalysis was entirely negative. Further improvement in renal function had taken place, and the values for inulin and para-aminohippuric acid clearance were near the lower limits of normal. The maximum specific gravity was now 1.023.

DISCUSSION

The data presented above indicate that the 5 patients all suffered from a significant impairment of renal function that was associated with potassium

depletion. In 4 subjects the renal function returned to normal, or nearly to normal, after potassium balance had been restored. In the fifth (Case 3) renal function was only partially restored, but this was probably related to the complicating factor of chronic pyelonephritis, as well as to the fact that complete restoration of potassium balance could not be achieved during the period of observation. The relation of renal function to potassium balance was perhaps most convincingly demonstrated by Case 2, whose renal function was severely impaired on two occasions while she was depleted of potassium and then each time rapidly improved after the potassium deficit had been corrected.

A temporal relation between renal impairment and potassium depletion does not necessarily prove that they are causally connected, and it needs to be asked whether factors besides potassium depletion could have been involved. The data presented here do not permit an unequivocal answer to this question, but considerable evidence can be marshaled in support of a primary role for potassium. None of the extrarenal factors known to produce reversible impairment of kidney function were present. Sodium depletion, dehydration, circulatory insufficiency, alkalosis, hypercalcemia and urinary obstruction could all be satisfactorily excluded on the basis of clinical or laboratory evidence. With the exception of Case 1, who gained a moderate amount of weight over the course of a year and a half, none of the subjects showed any appreciable change in nutritional state during the period of observation when renal function was improving. Further support for the hypothesis that potassium depletion is a specific cause of renal dysfunction is afforded by the observation that the maximum transport of para-aminohippuric acid by rabbit-kidney slices depends on optimal concentrations of potassium in the incubation medium or slices.[9] There is, also, suggestive evidence that experimental potassium depletion in rats may reduce glomerular filtration rate.[10]

In 1 subject (Case 1) serum magnesium was determined before and after restoration of the potassium deficit and it was found to be low during the period of depletion. This raises the possibility that some or all of the present patients were deficient in magnesium as well as potassium. There is some evidence, still incomplete, that experimental magnesium depletion may cause renal lesions,[11,12] and it is possible that this factor was involved in the production of the nephropathy. However, magnesium loss does not occur in experimental potassium depletion,[13] which has clearly been shown to produce renal lesions as well as functional impairment. It therefore seems

TABLE 1. *Renal-Function Data in Case 2.*

DATE	SERUM POTASSIUM	BLOOD UREA NITROGEN	INULIN CLEARANCE	CREATININE CLEARANCE	PARA-AMINOHIPPURIC ACID CLEARANCE	TUBULAR EXTRACTION RATIO FOR PARA-AMINOHIPPURIC ACID	TRUE RENAL PLASMA FLOW	MAXIMUM SECRETION OF PARA-AMINOHIPPURIC ACID	MAXIMUM SPECIFIC GRAVITY*	UREA CLEARANCE	15-MIN. PHENOLSULPHONPHTHALEIN EXCRETION
	milli-equiv./liter	*mg./100 ml.*	*ml./min.*	*ml./min.*	*ml./min.*		*ml./min.*	*mg./min.*		*% normal*	*%*
1st admission:											
1/16/52†	1.6-2.3	—	43	56	315	—	—	45	1.005	—	—
2/5/52‡	4.5	—	72	88	376	0.71	530	55	1.015	—	—
3/21/52‡	4.4	—	103	125	584	—	—	71	1.025	—	—
2d admission:											
7/21/55†	2.3	27	—	—	—	—	—	—	1.005	25	16
9/12/55‡	4.9	23	—	—	—	—	—	—	1.015	41	34
11/10/55‡	5.5	13	—	—	—	—	—	—	1.021	60	30

*After vasopressin stimulation.
†Before potassium therapy.
‡After potassium therapy.

FIGURE 4. *Biopsy of the Kidney Cortex in Case 2, during Severe Potassium Depletion, Showing Striking Dilatation of the Proximal Tubules, with Atrophy of the Epithelial Cells.*

reasonable to hypothesize that potassium was the prime factor in the present cases.

Detailed analysis of the renal-function data reveals a fairly consistent pattern in all patients. Although the levels of blood nonprotein nitrogen were not significantly elevated in any subjects, all were found to have some reduction in the clearance of the nitrogenous substances normally excreted chiefly by glomerular filtration, such as urea and creatinine. Inulin clearance, measured in four patients, was also reduced. Tubular function was even more strikingly impaired, as indicated in all 5 patients by the virtual absence of concentrating ability under vasopressin stimulation, and in 4 patients by a marked reduction in phenol-red excretion.

Routine urinalysis disclosed relatively slight evidence of disease. Minimal albuminuria and cylindruria were present in 3 patients, and only 1 (Case 2) had abnormal numbers of red or white blood cells in the spun sediment.

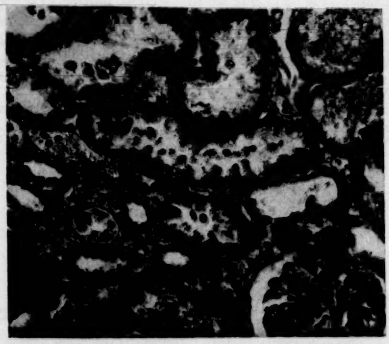


FIGURE 5. *Biopsy of the Kidney Cortex in Case 3 during Severe Potassium Depletion, Showing Diffuse Degeneration of the Tubular Epithelium, with Swelling and Pseudopodal Projections of Cytoplasm into the Tubular Lumens. Some other areas of the specimen showed slight, chronic pyelonephritic scarring.*

The recent clinical literature contains reports of at least 8 documented cases of severe and relatively uncomplicated chronic potassium depletion* in which there are sufficient clinical and laboratory data to permit comparison with the present group of patients.[4-7,14-16] Table 3 summarizes the pertinent data in this group. In 5 of the 7 patients there was fairly clear-cut evidence of a renal disorder, with definite abnormality in one or more tests of tubular or glomerular function. Frank azotemia occurred in only 1 patient (Case A). In the 2 patients studied before and after correction of potassium deficiency (Cases G and H) renal function appeared to improve, and in none was there any evidence of other causes for renal failure. The specific gravity of all random samples of urine was never more than 1.014, and in 2 patients whose concentrating ability was tested (Cases C and G) the specific gravity did not exceed 1.011. Minimal albuminuria was present in 6 patients. Abnormal formed elements were found in the urinary sediments of 5. Thus, considering both the patients described in the present study and the group collected from the literature, it appears that a fixed specific gravity is the most common clinical sign of renal disease. Minimal albuminuria occurs frequently, but significant abnormalities in the urinary sediment are less common. Although urea or creatinine clearance may be reduced, marked azotemia is uncommon.

FIGURE 6. *Biopsy of the Kidney Cortex in Case 3 after Partial Replacement of Potassium. The tubular epithelium is now essentially normal.*

Marked polyuria was noted in 5 of the combined group of 13 patients. In 1 of the cases reported above (Case 1) this symptom was severe enough to suggest diabetes insipidus. Slight to moderate peripheral edema was also noted in 5 patients. A tendency to retain ingested sodium chloride is apparently a common feature of severe potassium depletion[8,17] and does not seem to be explained by hypoproteinemia or congestive heart failure. Conceivably, the disturbance in renal function might have been responsible for sodium retention. On the other hand, the observations of Fourman and Hervey[17] in normal subjects experimentally depleted of potassium demonstrate that sodium retention may occur without obvious change in the usual clinical tests of renal function.

Discussion of the clinical and functional renal abnormalities in potassium depletion naturally leads to a consideration of the associated renal lesion. It has long been known that uncomplicated potassium depletion in rats produces a spectrum of lesions in the epithelium of the convoluted and collecting tubules, including cloudy swelling, extensive vacuoli-

*A determination of serum potassium was not made in 1 of these cases (Case F), but the clinical history of chronic diarrhea, the development of muscle paralysis shortly before death and the striking vacuolar renal tubular lesions constitute strong evidence of severe potassium depletion.

zation, fatty and calcific degeneration, necrosis and atrophy.[1-3] Perkins, Petersen and Riley[5] were the first workers clearly to attribute a renal tubular lesion in man to potassium deficiency. No renal-function studies were carried out in their patient disclosed marked vacuolization of the type described by Williams and MacMahon and by Perkins, Petersen and Riley. In the other 2 (Cases C and D) "granular cytoplasmic disintegration" was found, together with a few vacuoles in 1. In the present study

TABLE 2. *Renal-Function Data in Case 5.*

DATE	SERUM POTASSIUM	INULIN CLEARANCE	CREATININE CLEARANCE	SERUM CREATININE	PARA-AMINO-HIPPURIC ACID CLEARANCE	MAXIMUM SPECIFIC GRAVITY*	15-MIN. PHENOL-SULFONPHTHALEIN EXCRETION	NONPROTEIN NITROGEN
	milliequiv./liter	*ml./min.*	*ml./min.*	*mg./100 ml.*	*ml./min.*		*%*	*mg./100 ml.*
5/29/52†	2.0	43	42	1.19	88	1.008	3	45
6/20/52‡	4.8	70	93	0.57	403	1.017	21	42
7/22/52‡	5.1	80	103	0.52	407	1.023	—	34

*After vasopressin stimulation.
†Before potassium therapy.
‡After potassium therapy.

(Case B, Table 3), but autopsy disclosed extensive nonfatty degeneration of the convoluted tubules, varying from slight vacuolization to extensive necrosis and sloughing of epithelial cells. The authors recognized the similarity between these changes and those previously reported in potassium-depleted animals, and they suggested that the lesion in their case renal biopsies were carried out in 3 patients. The first biopsy during potassium deficiency in Case 1 revealed a diffuse foamy change in the tubular cytoplasm (Fig. 1), but in the second biopsy (Fig. 2) the more distinctive, large, clear vacuoles were abundant and were seen side by side with the diffuse degenerative changes. The initial biopsies in the other

TABLE 3. *Cases of Potassium-Depletion Nephropathy Collected from the Literature.*

CASE NO.	SOURCE OF DATA	SERUM POTASSIUM	CAUSE OF POTASSIUM DEPLETION	POLYURIA	EDEMA	ALBUMINURIA	URINARY SEDIMENT
		milliequiv./liter					
A	Williams & MacMahon[4] (1947)	2.9-3.7	Chronic diarrhea, idiopathic	No	No	Present	Granular casts
B	Perkins et al.[5] (1950)	3.8	Chronic diarrhea, idiopathic	No	No	No	Normal
C (Case 1)	Luft et al.[6] (1951)	2.3-3.5	"Cryptogenic"	Yes	No	"Slight"	Few red & white blood cells
D (Case 2)		2.0	"Cryptogenic"	No	Yes	Present on 1 occasion	6-10 white blood cells & 2-3 red blood cells per high-power field
E	Keye[7] (1952)	1.3-3.6	Sprue syndrome	No	No	Present (+ test)	Intermittent microscopic hematuria & cylindruria
F	M.G.H. Case 40081[14] (1954)	(Not done)	Chronic diarrhea (? sprue)	Yes	Yes	Present (++ test)	2 white blood cells and many casts per high-power field
G	Conn[15] (1955)	1.6-2.5	Adrenocortical adenoma; aldosterone excess.	Yes	No	Present ("trace")	Normal
H	Kjerulf-Jensen et al.[16] (1951)	1.4-4.9	Unknown, but extrarenal (urinary potassium excretion 3 milliequiv./day)	Yes	Yes	No data	No data

was similar to that found by Williams and MacMahon[4] a few years earlier in a patient with chronic diarrhea and hypokalemia (Case A, Table 3). In this case, there was marked vacuolization of the epithelium in the proximal tubules, which did not stain for fat or glycogen. In both patients, just as in potassium-depleted rats, glomeruli, interstitial tissue and blood vessels were essentially normal.

In 5 of the other 6 cases collected from the literature (Table 3) autopsy or biopsy examination of the kidney was made, and in each case significant tubular lesions were found. Three cases (Cases E, F and G) 2 patients showed definite but nonspecific degenerative cytoplasmic lesions. These might easily have been passed over without comment if they had not been examined within the context of the clinical situation. Although 3 patients represent an inadequate sampling, it seems probable that disturbances in renal function with potassium depletion occur more often than lesions that are sufficiently distinctive to attract attention. However, the disappearance of both the vacuolar and the nonspecific degenerative tubular changes after repair of the potassium deficit in Case 1 and Case 3 lends support to the hypothesis

that both lesions were in fact related to potassium deficiency.

In view of the changes in the tubular epithelium produced by potassium depletion it is not surprising that tubular dysfunction should be evident in these patients. On the other hand there is no morphologic evidence of glomerular or vascular injury to explain the marked reductions in the clearance of inulin, creatinine or urea. The absence of such overt damage does not, of course, exclude the possibility of more subtle lesions not demonstrable by the usual histologic methods. Moreover, alterations in circulatory dynamics conceivably could have reduced glomerular filtration rate even without a glomerular or vascular lesion. The low values for para-aminohippuric acid clearance in all 5 of our patients might be construed as supporting this possibility, but without measurement of tubular extraction the renal clearance of para-aminohippuric acid cannot safely be taken as an accurate measure of plasma flow. Para-aminohippuric acid extraction was low in the only case in which it was determined (Case 2). True plasma flow was therefore higher than clearance of para-aminohippuric acid and at the lower limit of normal. It is evident that more extraction data are required to determine the effect of potassium depletion on renal plasma flow.

The low clearance of inulin, urea and creatinine, although probably indicative of a reduced filtration rate, might alternatively be explained by back diffusion of these substances through damaged tubular epithelium. In such a situation the estimated clearances might be considerably less than the true rate of glomerular filtration. In the absence of more information all these questions must remain unresolved for the present.

Considering the relative frequency with which severe chronic potassium depletion occurs, it might at first seem surprising that the renal dysfunction associated with this condition has not been more widely recognized. It is probable that the clinical manifestations of the disease have been overlooked because they are ordinarily neither striking nor particularly specific. Furthermore, potassium depletion so often occurs in situations complicated by many other factors capable of producing renal disturbances that its special significance might easily go unnoticed. That the nephropathy of potassium depletion does actually occur frequently and in a wide variety of circumstances is suggested by the fact that a distinctive vacuolar lesion of the type referred to in this study has been noted by numerous pathologists in a considerable number of clinical states, particularly in severe diarrheal diseases. These vacuolar lesions have been well described, and the subject thoroughly reviewed by Kulka, Pearson and Robbins.[18] The lack of data on potassium metabolism in all these earlier cases allows only speculation on the relation of these lesions to potassium deficiency. Nevertheless, it is well known that potassium depletion commonly develops in the course of intractable or fatal diarrheal diseases, and it is not unreasonable to assume that these patients were potassium deficient. The frequency with which diarrhea produces this disorder is also suggested by the fact that all 5 patients described in the present study, as well as at least 4 of the 8 summarized in Table 3, were also suffering from chronic diarrhea of one type or another.

Table 4 lists all the disorders in which distinctive vacuolar lesions have been observed. It is obvious that the nephropathy of potassium depletion is not con-

TABLE 3 *(Concluded).*

CASE NO.	MAXIMUM SPECIFIC GRAVITY	RENAL FUNCTION	KIDNEY PATHOLOGY
A	1.011	Nonprotein nitrogen 95-144 mg. & creatinine 5.0 mg./100 ml.	Extensive vacuolization of all proximal convoluted tubules
B	1.012	No data	"Marked hydropic degeneration" of convoluted tubules, varying from slight vacuolization to complete necrosis and sloughing; "slight epithelial proliferation in Bowman's capsule."
C (Case 1)	1.011 (concentration test)	Nonprotein nitrogen 41 mg./100 ml.; inulin clearance 58 ml. & Diodrast clearance 362 ml./min./1.73 m²; impaired water diuresis.	"Granular cytoplasmic disintegration"; "few large vacuoles in convoluted tubules"; also, "focal tubular disintegration & scarring."
D (Case 2)	1.014	Nonprotein nitrogen 34 mg./100 ml.	"Slight swelling & granular cytoplasmic disintegration of convoluted tubules"
E	1.000	Nonprotein nitrogen 45 mg./100 ml.; normal intravenous pyelogram.	"Marked vacuolization of tubular epithelium," with "occasional necrosis & shedding" of epithelium; some vacuoles stained for fat.
F	Not reported	Nonprotein nitrogen 35 mg./100 ml.; phenolsulfonphthalein excretion 20% in 30 min.	Marked vacuolization of convoluted tubules
G	1.011 (vasopressin)	Nonprotein nitrogen 33-38 mg./100 ml.; creatinine clearance 87-118 ml./min.; phenolsulfonphthalein excretion 50% in 30 min.	"Diffuse vacuolar change in tubular epithelium," with some necrosis & calcification
H	1.012	Blood urea nitrogen 32 mg./100 ml.; urea clearance 27 ml./min.; after potassium therapy, urea clearance 75 ml./min.	No data

fined to intestinal disorders. Vacuolar lesions have been observed in a patient with primary aldosteronism (Case G, Table 3) and they have also been noted in 2 patients who were treated with large doses of cortisone.[19] In another group of patients, the distinctive lesions of potassium depletion have apparently developed as a secondary complication in

TABLE 4. *Clinical States with Renal Lesions Probably Due to Potassium Depletion.*

DIARRHEAL DISEASES[18,26]:
Ulcerative colitis
Regional enteritis
Cholera
Bacillary dysentery
Sprue syndrome
Whipple's disease
Malabsorption syndrome
HYPERADRENALISM:
Cortisone treatment[19]
Primary aldosteronism[15]
RENAL DISEASE WITH URINARY POTASSIUM WASTING:
Fanconi syndrome[21]
Renal tubular acidosis[20]
Cystinosis[22]
RENAL DISEASE WITH EXTRARENAL POTASSIUM WASTING:
Subacute glomerulonephritis[25]
Chronic glomerulonephritis & lower-nephron nephrosis[24]
Chronic pyelonephritis & hydronephrosis[25]
VERSENE POISONING[23]

kidneys already diseased. There are in the literature at least three reports of renal tubular vacuoles in children with primary renal tubular disease who probably were potassium depleted at least partly as the result of urinary wasting.[20-22] Similar tubular lesions have also been described in a patient who became potassium depleted after the administration of a chelating agent that caused tubular necrosis[23] and in another patient with chronic glomerular nephritis[24] who became hypokalemic after an episode of prolonged vomiting and diarrhea. We have also noted these distinctive large vacuoles in the kidneys of 1 patient with subacute glomerulonephritis and another with pyelonephritis, both of whom became potassium depleted as the result of vomiting and diarrhea. It may confidently be predicted that this list will grow longer as the nature and significance of these lesions become more widely appreciated. Furthermore, since severe potassium depletion may seriously impair renal function without producing distinctive tubular lesions, it seems probable that the functional disorder will prove to be far more common than any change in tubular histology detectable by routine methods.

It would now seem justified to add potassium depletion to the list of possible causes of reversible renal damage. Potassium depletion may severely impair tubular function, but by itself it apparently is not apt to produce overt uremia. The functional consequences of potassium depletion are probably most important when it occurs as a complication of pre-existing renal disease. The additional insult of potassium depletion might well pass unrecognized, and progressive renal impairment might be attributed to extension of the underlying kidney disorder. Potassium depletion probably is also an important contributing factor in the uremia observed in patients with multiple electrolyte deficiencies, such as gastric alkalosis,[27] and the various depletion states produced by loss of gastrointestinal secretions.

On the other hand, the nephropathy of potassium depletion might easily be confused with chronic pyelonephritis or glomerulonephritis in a polyuric, preuremic phase, particularly in cases of potassium depletion accompanied by albuminuria or cylindruria. The difficulty of distinguishing between primary renal disease and renal impairment resulting from potassium depletion is well illustrated by the recent reports of so-called "potassium-wasting nephritis."[28-31] The subjects of these reports had marked hypopotassemia and a pattern of renal dysfunction similar to that reported here (that is, isosthenuria, but little or no uremia). In each case urinary wasting of potassium was demonstrated, and it was suggested that a primary renal tubular disease was responsible. Although this explanation is not unreasonable, it seems at least as likely that, as suggested by Conn,[15] the potassium loss was due to primary aldosteronism. In that event, the entire renal disorder might be secondary to the potassium deficiency. This concept is supported by the improvement in function that followed administration of potassium in 2 of these cases.[28,31] Regardless of whether primary renal disease was responsible for the potassium loss in this group, there is no doubt that potassium depletion, either renal* or extrarenal, can of itself impair renal function. This needs to be considered whenever potassium depletion exists in a patient with renal dysfunction.

Clinical diagnosis of the nephropathy of potassium depletion appears at present to rest mainly on the demonstration of the association of renal dysfunction with potassium depletion and on the improvement in function that follows restoration of potassium balance. In this connection, it must be remembered that a normal level of potassium in the serum does not rule out potassium depletion, and that the functional consequences of this syndrome may persist long after serum potassium concentration has been restored to normal.

A number of pertinent problems remain to be considered. The minimum severity and duration of the potassium deficits necessary to produce the renal lesions or the functional disturbances in man are not known. In general, the patients in our group had

*There is no evidence at present that urinary wasting of potassium can result from the nephropathy of potassium depletion. In 4 of the 5 cases reported here twenty-four-hour collections of urine were obtained during the phase of potassium depletion, and in all of them excretion of potassium was less than 10 milliequiv. per day. Despite the evidence of severe impairment of tubular function in these patients, they appeared to be capable, at least ultimately, of a normal response to the need for conservation.

suffered from severe prolonged depletion lasting months or years, but the clinical history in several of the autopsied cases (Table 4) suggests that the vacuolar lesion may develop within the course of a few weeks. The healing process appears to be a gradual one, even in patients whose potassium deficits are fully restored. Thus, in Cases 2 and 4, normal function was not restored until six weeks to three months after potassium depletion had been corrected. Although the disorder appears to be completely reversible, at least at some stage and in some patients, it is not known whether permanent irreversibie or progressive renal disease can result. More observations on clinical and experimental potassium depletion will be required to answer these and the many other questions raised by the present study.

Summary and Conclusions

The clinical features of a previously unrecognized disorder of renal function associated with potassium deficiency are defined in a group of 5 patients with severe chronic potassium depletion.

In each case potassium depletion had resulted from chronic diarrhea. Severe hypokalemia was the rule, but no patient was dehydrated or sodium depleted, and none had significant acid-base disturbances. There was no evidence of renal wasting of potassium. One patient noted marked polyuria.

Blood nonprotein nitrogen levels were normal or only slightly elevated, but all patients exhibited vasopressin-resistant hyposthenuria. Clearances of inulin, endogenous creatinine and para-aminohippuric acid were significantly reduced. Routine urinalysis revealed minimal inconstant albuminuria and cylindruria in 3 cases.

Replacement of potassium deficits resulted in gradual restoration of normal renal function in 4 and moderate improvement in a fifth patient.

Renal biopsies obtained in 3 patients showed hydropic and degenerative changes confined chiefly to the convoluted tubules, without significant glomerular or vascular disease. In 1 case there was striking vacuolization of the tubules. Restoration of potassium balance produced total healing of the lesions in 1 patient and marked improvement in another.

From a consideration of these data and a survey of the evidence in the literature, it is concluded that the nephropathy of potassium depletion is a relatively common clinical and pathological entity that may complicate a variety of situations. Potassium depletion apparently should be added to the list of causes of reversible renal disease.

We are indebted to Drs. H. E. MacMahon and C. S. Sommers, pathologists at the New England Medical Center and the Massachusetts Memorial Hospitals, respectively, for their valuable assistance with the interpretation of the biopsy material. Dr. MacMahon was also kind enough to provide most of the photomicrographs. We are also indebted to Drs. C. W. Robertson and B. G. Clarke, who performed the surgical biopsies for us, and to Dr. R. M. Kark, who carried out the needle biopsy in Case 3.

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ANGIOCARDIOGRAPHY IN THE DIAGNOSIS OF SACCULAR ANEURYSM OF THE ABDOMINAL AORTA*

Report of a Case

ISRAEL STEINBERG, M.D.,† AND NATHANIEL FINBY, M.D.‡

NEW YORK CITY

RECENTLY, Vaughan and his associates[1] described the successful excision under emergency conditions of an aneurysm of the abdominal aorta that was explored with the preoperative diagnosis of a paraspinal tumor. In the discussion of the case, the authors stated that angiocardiography, if it had been done, would have disclosed the aneurysm, and more successful preparation could then have been made for definitive surgery. This proved to be the situation in the case reported below. Once angiocardiography had established the diagnosis of a saccular aneurysm of the aorta eroding the bodies of the twelfth dorsal and first lumbar vertebras, surgical excision of the aneurysm and suture of the aorta were readily achieved.

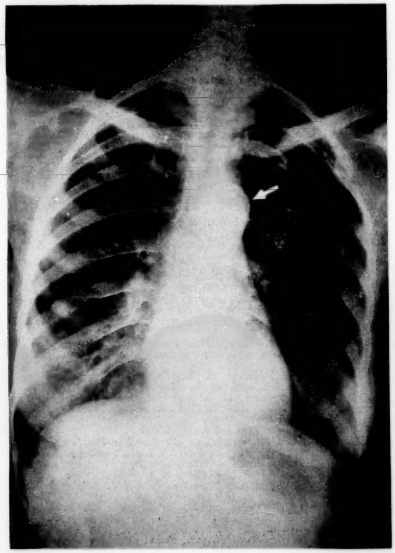


FIGURE 1. *Conventional Frontal Roentgenogram of the Chest, Showing a Normal Appearance except for Calcific Deposits in the Aortic Knob (Arrow).*

CASE REPORT

A 51-year-old Negress (N.Y.H. 661260) was admitted to the hospital on July 10, 1953, complaining of pain in the lower back and urinary incontinence of 8 months' duration. At onset, the backache was slight but increased in severity and became constant. Urinary incontinence developed at the same time, and an anterior colporrhaphy was done at another hospital several months before admission, without relief of pain or incontinence.

Physical examination revealed a poorly nourished but well developed woman with moderate discomfort due to pain in the lower back. The pupils were regular and reacted to light and accommodation; the fundi showed arteriolar thickening and arteriovenous nicking. The chest was clear. The heart was not enlarged; the rate was 72 and regular.

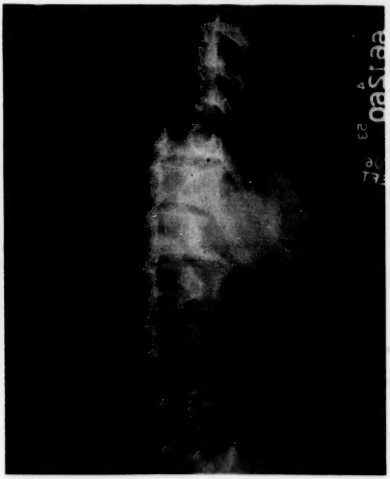


FIGURE 2. *Oblique Roentgenogram of the Spine, Showing Marked Erosion of the Bodies of the Twelfth Thoracic and First Lumbar Vertebras.*

An adjacent mass contains calcifications (arrow).

The aortic 2d sound was louder than the pulmonic. The wrist, femoral and dorsalis-pedis vessels were palpable and not sclerotic. The blood pressure was 118/70. No abnormal masses, pulsations or bruits were present in the abdomen. Vaginal examination revealed that the uterus and adnexa were absent (a hysterectomy had been performed 6 years previously).

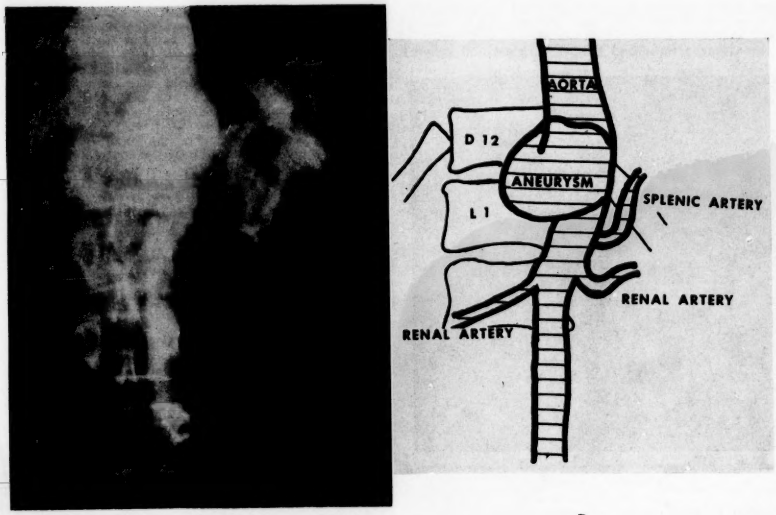
Neurologic examination established the pain as being in the lower lumbosacral region, with girdlelike radiation

*From the Department of Radiology, New York Hospital-Cornell Medical Center.

Aided by a grant from the Mallinckrodt Chemical Works.

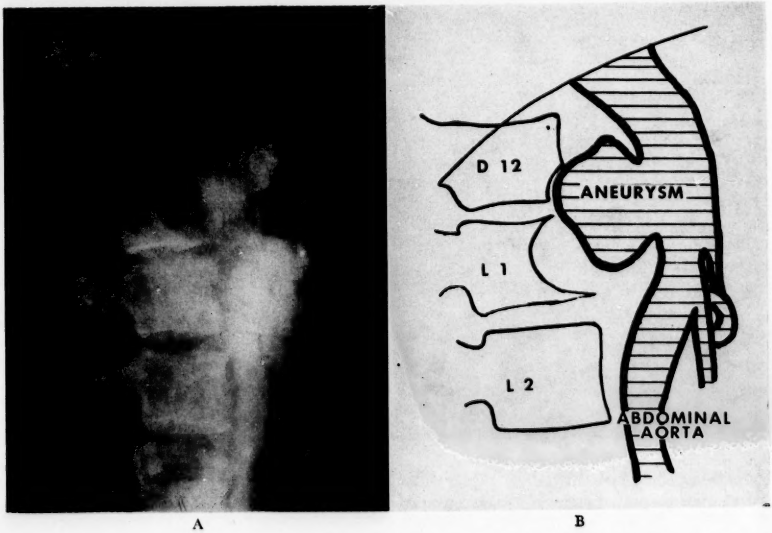
†Assistant clinical professor of medicine and radiology, Cornell University Medical College; assistant physician and radiologist, New York Hospital.

‡Instructor in radiology, Cornell University Medical College; radiologist, New York Hospital.



A B

FIGURE 3. *Angiocardiogram* (A), *Taken with the Patient Supine, Showing a Saccular Aneurysm of the Abdominal Aorta Adjacent to the Eroded Vertebral Bodies, with a Tracing of the Aneurysm* (B).



A B

FIGURE 4. *Lateral Angiocardiogram* (A) *of the Thoracolumbar Portion of the Aorta, Further Demonstrating the Saccular Aneurysm and Its Relation to the Spine, with a Tracing of the Aneurysm* (B).

around to the anterior and lateral portions of the abdomen. The spine was straight, and there was no pain on forward flexion; extension caused lumbosacral pain, but flexion of the spine to the right and left was normal and painless.

FIGURE 5. *Photograph of the Excised Aneurysm and Thrombus (Arrow).*

Tenderness to fist pressure was present over the lumbosacral junction. The gait was normal, and there was no weakness of the lower extremities. The abdominal and lower-limb reflexes were brisk, equal and sustained. The Babinski sign was positive on the right. Pinprick, cotton, position, vibratory and temperature sensations were intact.

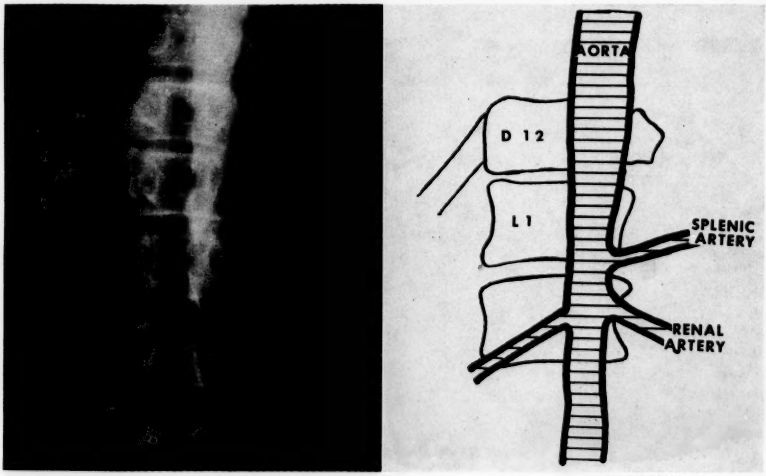
Laboratory examination showed negative blood and spinal-fluid serologic tests for syphilis (Mazzini, Wassermann and Kolmer procedures). X-ray examination of the chest revealed clear lung fields, with a normal heart but large calcific deposits in the aortic arch (Fig. 1). X-ray examination of the spine demonstrated a rounded, 6-cm. mass containing calcium, located to the left of the junction of the dorsolumbar spine, associated with marked erosion of the bodies of the 12th dorsal and 1st lumbar vertebras (Fig. 2). Angiocardiography was performed in frontal and lateral views, with the patient reclining on a Fairchild roll-film magazine. Exposures made at ½-second intervals, beginning 8½ seconds after the onset of the injection, revealed a large saccular aneurysm of the aorta containing laminated clot (Fig. 3 and 4).

At operation* on July 30, a left-flank incision was made, and a pulsatile, saccular aneurysm, 5 by 10 cm., containing blood clots, was found. Erosion of 2 vertebral bodies was also seen. The mouth of the aneurysm measured 3 by 1.5 cm. The aorta was sclerotic but free, pliable and mobile. After the aorta had been clamped, the aneurysm was easily removed. A 0.5-cm. cuff and suture of the aorta with No. 00000 silk were then readily accomplished.

Pathological study† revealed an aortic aneurysm measuring 4 x 7 cm. (Fig. 5). Well organized (9 by 5 by 4 cm.) and partially organized (2.5 by 3.0 cm.) thrombi were contained in the aneurysm. Microscopical examination of the wall of the aneurysm disclosed considerable scar tissue and calcification. Hemosiderosis and calcification were found in the media; organized thrombus was attached to the intima. The clot contained layers of acellular fibrin.

The postoperative course was uneventful, and the patient was up and about on the 11th day. An angiocardiogram on August 20 (Fig. 6) revealed a normal aortic lumen. On account of urinary incontinence she was transferred to the urologic service. On August 25, cystopexy was performed. Recovery was uneventful and she was discharged on September 6. There was complete subsidence of the back pain.

Subsequently, on November 5, she was readmitted to the hospital because of continuing incontinence. An exploratory laparotomy was done on November 20, in the hope of alleviating the incontinence. No abnormalities were found, and the cystopexy was found to be satisfactory. She was



A B

FIGURE 6. *Postoperative Angiocardiogram* (A), *Showing the Intact Aorta, with a Tracing of the Aorta* (B).

*Performed by Dr. S. W. Moore.
†Performed by Dr. John M. Pearce.

discharged on December 11, without improvement of the incontinence. She was subsequently seen several times in the outpatient department, where marked mental depression became evident. In March, 1954, she was committed to a state psychiatric hospital; a communication in July, 1955, disclosed that she was still an inmate of the hospital.

Discussion

In contrast to the case reported by Vaughan et al.,[1] in which syphilis was the cause of the saccular abdominal aneurysm, this patient's aneurysm was due to arteriosclerosis. Bone erosion by an arteriosclerotic aneurysm of the abdominal aorta is rare because lengthening, dilatation and tortuosity of the arteriosclerotic aorta usually prevent contact with the spine.[2] Only 1 case of erosion involving the body of the twelfth dorsal vertebra was discovered in Crane's[3] series of 44 patients. When bone erosion occurs, it is believed to be the effect of the pounding aneurysm, which is held down against the spine by the diaphragmatic hiatus and renal arteries.[2,3]

Suspicion of the presence of an aortic aneurysm was deduced from the x-ray examination of the thoracolumbar spine, which revealed marked erosion of the bodies of the 12th dorsal and 1st lumbar vertebras, without apparent involvement of the intervertebral disks (Fig. 2). In addition the mass in the vicinity of the bone lesions contained calcium. These findings were in distinct contrast to the case of Vaughan et al.,[1] in which the aneurysm was not discovered until exploratory operation.

Visualizing the entire abdominal aorta by angiocardiography is usually unsatisfactory because opacification is often insufficient. However, aneurysms in the thoracolumbar portion of the aorta, especially when multiple films are used[4] (Fig. 3-5), may be expected to be well visualized.

Surgical excision of a saccular aneurysm of the aorta, with suture of the mobilized aorta, has become an accepted technic.[1,5] Homografts or plastic materials may be necessary if there is extensive disease of the aorta. Visualization of the aorta before surgery is desirable, not only for diagnosis but also to permit planning of the surgical attack.

Summary

A case in which the diagnosis of a large saccular aneurysm of the aorta eroding the bodies of the twelfth dorsal and first lumbar vertebras was made after angiocardiography is reported. This facilitated surgical treatment.

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ABSORPTION, ELIMINATION AND EXCRETION OF ORALLY ADMINISTERED VITAMIN B_{12} IN NORMAL SUBJECTS AND IN PATIENTS WITH PERNICIOUS ANEMIA*

Myron Pollycove, M.D.,† and Leonard Apt, M.D.‡

With the Technical Assistance of
Mary Pratt, M.A., Joan Donovan, B.A., and Jack Sullivan, B.S.

BOSTON

A SELECTIVE defect of Vitamin B_{12} absorption is pathogenic of Addisonian pernicious anemia. The parenteral administration of crystalline vitamin B_{12} in daily doses of 1 to 5 microgm. to patients with pernicious anemia in relapse has been shown to produce a characteristic, optimal hematopoietic response.[1-5] Oral administration of crystalline vitamin B_{12} in daily doses of 5 microgm. to patients with pernicious anemia in relapse produces little or no hematopoietic response unless a source of intrinsic factor is administered either simultaneously or within six hours.[6,7] This persistent inability of patients with Addisonian pernicious anemia to absorb from the gastrointestinal tract the vitamin B_{12} in their daily food (approximately 5 to 15 microgm.) is the derangement that eventually results in a vitamin B_{12} deficiency state manifested clinically in many ways. The desirability of measuring the absorption of the dietary intake of vitamin B_{12} is evident. Efforts to do this by measurement of blood and urine with standard microbiologic-assay procedures have not succeeded because of the minute change in the amount of vitamin B_{12} in the blood or urine after ingestion of dietary quantities. It has not been possible

*From the Radioisotope Unit and Medical Service, Boston Veterans Administration Hospital, and the Department of Medicine, Tufts University School of Medicine.

†Research associate, Donner Laboratory, University of California, Berkeley, California; formerly, teaching fellow in medicine, Tufts University School of Medicine, and resident in medicine, Medical Service, Boston Veterans Administration Hospital.

‡Formerly, staff physician, Radioisotope Unit, Boston Veterans Administration Hospital.

to bioassay the unabsorbed portion of oral doses of vitamin B_{12} eliminated in the feces because of the presence of large amounts of material with vitamin B_{12} activity thought to be synthesized by bacteria in the lower intestine.

The biosynthesis in 1950 of cobalt^{60}-labeled vitamin B_{12} with a relatively high specific activity[8,9] has made it possible to measure extremely minute amounts of this material. In this laboratory it is possible to measure within $\pm$ 30 per cent radioactive vitamin B_{12} at a concentration of 8 micromicrogm. per milliliter. Soon after its biosynthesis, Heinle and his colleagues[10] employed radioactive vitamin B_{12} to determine the fecal elimination of a small oral dose established in the 3 patients by the demonstration of the presence of a macrocytic anemia and a megaloblastic erythroid hyperplasia of the bone marrow before therapy, as well as by histamine-fast achlorhydria. Each underwent a complete hematopoietic response after parenteral administration of vitamin B_{12}.

Methods

Fecal Elimination of Orally Administered Cobalt^{60}-Labeled Vitamin B_{12}

The same lot of radioactive vitamin was used in the preparation of all the oral test doses: dissolved crystalline cyanocobalamin cobalt^{60} with a specific activity of 0.77 microcuries per microgram. A ten-day collection of stools was obtained by having the patient defecate directly into a previously tared 4-liter screw-cap jar to which a small amount of formol had been added. All stool specimens during the ten-day period were collected in a single jar. Upon completion of the collection, an appropriate amount of distilled water was added to produce a suitable consistence for homogenization. This jar was then capped with a lid in which rotor blades were mounted and placed in an Osterizer, and the contents thoroughly homogenized. The jar and its contents were weighed. Samples approximately 25 ml. in volume were removed to suitable, previously tared vials, and then placed within a shielded Geiger–Müller counter under conditions of constant geometry. The counts per minute above background thus obtained were multiplied by the ratio of the total weight of the homogenized fecal collection to the weight of the sample counted. The total counting rate of the fecal collection was compared with the similarly determined total counting rate of the oral dose administered at the beginning of the fecal collection and expressed as the percentage

Table 1. *Absorption of Orally Administered Radioactive Vitamin B_{12}.*

Subject	Percentage in Feces	Percentage Not in Feces	Percentage in Liver	Hepatic Deposition of Ingested Radioactive Vitamin *c.p.m./microcurie*	Hepatic Deposition of Injected Radioactive Vitamin *c.p.m./microcurie*	Percentage in Urine
Normal persons:						
N.Z.	18.1	81.9		4085		10.3
A.N.	37.9	62.1		5300		7.3
F.C.	31.2	68.8	71.0	4108	5750	8.7
Patients with pernicious anemia:						
S.N.	85.3	14.7	10.4	390	3742	0.6
S.N., with added gastric juice	42.4	57.6	67.9	2541	3742	
G.A.	93.0	7.0	6.2	286	4633	0.6
G.A., with added gastric juice	47.8	52.2	58.6	2713	4633	
G.P.	95.0	5.0	8.5	334	3926	1.0
G.P., with added gastric juice	36.0	64.0	70.9	2790	3926	

given alone or with a source of intrinsic factor to patients with pernicious anemia. In the following year Schilling,[11] by ingeniously employing a massive parenteral "loading" dose of nonlabeled vitamin B_{12}, was able to demonstrate the absorption or relative nonabsorption of small oral doses of radioactive vitamin by measuring the urinary excretion of the labeled vitamin B_{12}. A few months later Glass et al.[12] measured the gamma-ray emission of cobalt^{60} at the body surface over the liver after ingestion of the radioactive vitamin and thus demonstrated in still another way the absorption or relative nonabsorption of vitamin B_{12}.

The experiments described below were undertaken to compare quantitatively the values for absorption of vitamin B_{12} as determined by the methods mentioned above and to evaluate these technics of measuring vitamin B_{12} absorption. Three normal persons and 3 patients with pernicious anemia in complete remission were each tested for intestinal absorption of the radioactive vitamin by measurement of fecal elimination, urinary excretion and hepatic deposition of cobalt^{60}. The diagnosis of pernicious anemia was

of the ingested cobalt^{60}-labeled vitamin B_{12} eliminated in the feces during the following ten-day period.

Urinary Excretion of Orally Administered Cobalt^{60}-Labeled Vitamin B_{12}

Twenty-five-milliliter aliquots of a twenty-four-hour collection of urine were counted, and the determined total urinary counting rate compared with the total counting rate of the oral dose of radioactive vitamin administered at the beginning of the urine collection. The counter described above was employed.

Hepatic Deposition of Cobalt^{60} after Oral Administration of Cobalt^{60}-Labeled Vitamin B_{12}

The crystal of a mobile scintillation counter head was placed on the skin of the subject overlying the middle of the liver in the mid-axillary line. A similar application to the lower left thigh was used to determine the background counting rate. In this manner hepatic counts per minute per microcurie of admin-

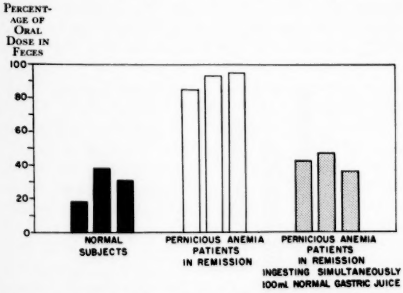

FIGURE 1. *Absorption of Vitamin B_{12} As Measured by Fecal Elimination of 0.5 Microgm. of Ingested Cobalt^{60}-Labeled Vitamin B_{12} in a Ten-Day Stool Collection.*

istered cobalt^{60}-labeled vitamin B_{12} were obtained before and ten days after ingestion. To obtain the hepatic counting rate resulting from "complete absorption," the procedure described above was subsequently repeated with the use of subcutaneous injection of an equal dose of radioactive vitamin. The hepatic counting rate after ingestion was compared with the hepatic counting rate after injection to determine the percentage of the orally administered radioactive vitamin that had been absorbed.

Experimental Procedures

Three patients with pernicious anemia in complete remission, and 3 normal persons were each monitored over the liver and thigh. They then received an oral dose of 0.5 microgm. of cobalt^{60}-labeled vitamin B_{12}. During the subsequent ten days stool collections were obtained in the manner stated above, and the fecal elimination of the oral dose determined. At the conclusion of this ten-day period the hepatic deposition of cobalt^{60} was ascertained. The same procedure was then repeated in the patients with pernicious anemia, 100 ml. of normal human gastric juice being administered simultaneously with the oral dose of 0.5 microgm. of radioactive vitamin. The urinary excretion was determined in the 6 subjects as follows. After a control specimen had been collected each subject was given an oral dose of 2.0 microgm. of cobalt^{60}-labeled vitamin B_{12}, and at the same time

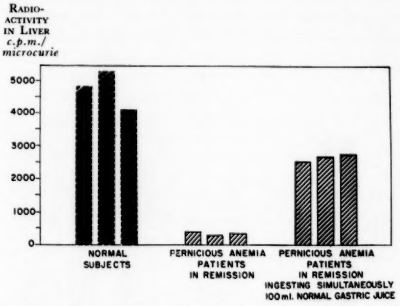

FIGURE 2. *Absorption of Vitamin B_{12} As Measured by Hepatic Deposition of Cobalt^{60} after Ingestion of 0.5 Microgm. of Cobalt^{60}-Labeled Vitamin B_{12}.*

1000 microgm. of unlabeled vitamin was injected subcutaneously. All urine passed during the next twenty-four hours was obtained from each subject, and the excretion of the orally administered vitamin determined. After the liver and thigh had been monitored, 1 normal subject and 3 patients with pernicious anemia were given a subcutaneous injection of 0.5 microgm. of cobalt^{60}-labeled vitamin B_{12}, and the hepatic deposition of the parenterally administered cobalt^{60} determined. Monitoring the injection sites before and shortly after injection, as well as ten days later, indicated that no significant activity remained at the injection site at the latter time.

Results

The percentages of oral doses of 0.5 microgm. of cobalt^{60}-labeled vitamin B_{12} eliminated in the stool during the ten-day collection period by the 3 normal subjects and the 3 patients with pernicious anemia in complete remission are shown in Table 1 and Figure 1. Whereas the former eliminated 18 to 38 per cent of the administered dose in their feces, the latter eliminated 85 to 95 per cent of the administered dose. When 100 ml. of filtered, neutralized normal gastric juice was given simultaneously with the oral dose to the patients with pernicious anemia, only 38 to 48 per cent of the administered dose was eliminated in the feces (Table 1 and Fig. 1). It is assumed that

most of the vitamin B_{12} not eliminated in the feces was absorbed. These values are shown in Table 1.

The radioactivity measured at the body surface over the liver ten days after ingestion of 0.5 microgm. is shown in Table 1 and Figure 2. These data were obtained after the same oral dose simultaneously analyzed for the percentage eliminated in the feces. Normal individuals deposited enough cobalt^{60} in the liver to produce hepatic body-surface counts above background, ranging from 4085 to 5300 counts per minute per microcurie ingested, as contrasted with patients with pernicious anemia, whose hepatic body-surface counts ranged from 286 to 390 counts per minute per microcurie. The subsequent addition of

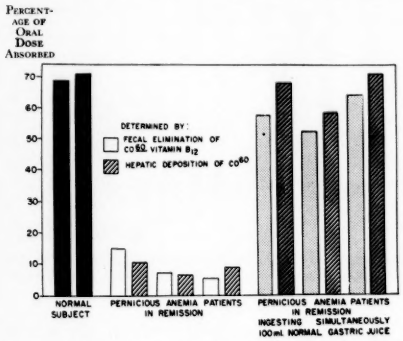

FIGURE 3. *Absorption of Vitamin B_{12} As Measured Simultaneously by Fecal Elimination of Vitamin B_{12} and Hepatic Deposition of Cobalt^{60} after Ingestion of 0.5 Microgm. of Cobalt^{60}-Labeled Vitamin B_{12}.*

100 ml. of normal gastric juice to an oral dose of 0.5 microgm. of cobalt^{60}-labeled vitamin B_{12} caused a rise of 2541 to 2790 counts per minute per microcurie. Ten days after the subcutaneous injection of 0.5 microgm. of radioactive vitamin, rises of hepatic body-surface counts varied from 3742 to 5750. No significant difference was found in hepatic deposition of cobalt^{60} between the normal persons and the patients with pernicious anemia when the vitamin was administered in this fashion. The percentage absorbed as determined by hepatic deposition is compared in Table 1 and Figure 3 with the corresponding percentage absorbed as calculated from measurements of fecal elimination. The values as determined simultaneously by the two methods are in fairly close agreement.

The twenty-four-hour urinary excretion of an oral dose of 2.0 microgm. of cobalt^{60}-labeled vitamin B_{12} administered simultaneously with a subcutaneous injection of 1000 microgm. of nonradioactive vitamin B_{12} is shown in Table 1 and Figure 4. The normal subjects excreted 7.3 to 10.3 per cent of the orally administered dose in the urine whereas the patients with pernicious anemia excreted only 0.6 to 1.0 per cent.

Discussion

The small dose of 0.5 microgm. of vitamin B_{12} was selected for administration because the percentage of larger doses absorbed by normal persons decreases even when a large quantity of normal human gastric juice is ingested simultaneously. Thus, as much as 70 per cent of a 5.5-microgm. dose of orally administered cobalt^{60}-labeled vitamin B_{12} may be eliminated in the feces of a normal person.[10] At the 0.5-microgm. level the range of fecal elimination for the normal subjects (18 to 38 per cent) and the patients with pernicious anemia (85 to 95 per cent) is in good agreement with that reported in similar studies.[10] The reduction of fecal elimination of the vitamin in patients with pernicious anemia when 100 ml. of normal human gastric juice was ingested simultaneously with the cobalt^{60}-labeled vitamin B_{12} suggests that the abnormally high fecal elimination of radio-

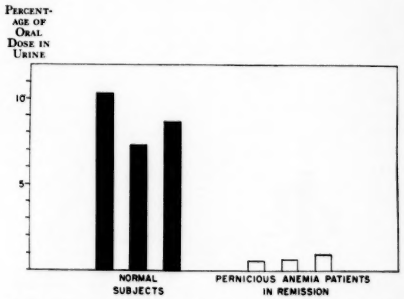

FIGURE 4. *Absorption of Vitamin B_{12} As Measured by Excretion of 0.5 Microgm. of Ingested Cobalt^{60}-Labeled Vitamin B_{12} in a Twenty-four-Hour Collection of Urine.*

active vitamin in these patients is due to a deficiency of intrinsic factor. The chief advantage of the fecal-elimination method of determining absorption is that it is a direct measurement of the amount of vitamin B_{12}, or at least of its cobalt moiety, eliminated. If the collection period is sufficiently long, the greater part of balance may be assumed to have been absorbed. The method has two minor disadvantages: ten days are required to ensure that no further radioactive vitamin will be eliminated after the collection is terminated; and the processing and counting of the stool collection takes time and is somewhat unpleasant. The major disadvantage, however, is the difficulty and uncertainty involved in obtaining a complete ten-day stool collection. To accomplish this a relatively long period of co-operation and vigilance is required from the subject during which he is greatly inconvenienced. Since the upper limit of the normal range

(45 per cent) is not far removed from the lower limit of the pernicious-anemia range (70 per cent),[10] the omission of a single critical bowel movement from the collection of a patient with pernicious anemia could easily lower the percentage of radioactive vitamin B_{12} recovered in the feces to the normal range.

The ranges of twenty-four-hour urinary excretion of orally administered vitamin B_{12} for normal persons (7.3 to 10.3 per cent) and patients with pernicious anemia (0.6 to 1.0 per cent) found in this study (Table 1 and Fig. 4) qualitatively confirm the results of Schilling[11] but are slightly at variance with his ranges for normal subjects (1.5 to 5.3 per cent) and patients with pernicious anemia (0 to 0.65 per cent). This method has the advantages of being relatively rapid and convenient in collection, processing and counting. In addition, the ranges of vitamin B_{12} excretion in the urine in normal subjects and patients with pernicious anemia are well separated from one another. The method has the disadvantages of being unsuited for measuring the percentage of the dose absorbed and of requiring a massive subcutaneous "flushing" dose of vitamin B_{12} that, by initiating maximal therapy prematurely in certain cases of pernicious anemia in relapse, may preclude other studies.

The premise that hepatic counting rates reflect the degree of absorption of cobalt^{60}-labeled vitamin B_{12} rests on the following observations of Glass[12] and our unpublished data.[13] Approximately a week after oral or parenteral administration of the radioactive vitamin to normal subjects or patients with pernicious anemia in remission the hepatic counting rate for gamma-ray emission of cobalt^{60} is maximal, and the liver is the only major site of deposition. During the subsequent thirty to one hundred days the hepatic counting rate remains above 90 per cent of the maximal rate attained at the end of the first week and at no other site is cobalt^{60} detectable. This apparently static deposition suggests that cobalt^{60} may be detached in some fashion from the vitamin B_{12} molecule and deposited in the liver while the physiologically active fraction of the vitamin B_{12} molecule travels elsewhere to perform its necessary functions. On the other hand, this may very well not be so, since normal human liver and the livers of patients with pernicious anemia who have received adequate treatment have been shown to contain sufficient amounts of potent material to keep other patients with pernicious anemia in remission for seven to thirty-six months.[14-16] Patients with pernicious anemia in relapse have had remissions persisting for two to twelve months after a single massive injection of 160 *U.S.P.* units of liver extract.[17] MacDonald, Ingelfinger and Belding[18] have noted that usually four or more years are required for pernicious anemia to develop after total gastrectomy when no vitamin B_{12} is administered parenterally. Halsted, Gasster and Drenick,[19] using the fecal-elimination method, have shown that the deficiency of intrinsic factor in patients after total gastrectomy is as complete as that existing in patients with pernicious anemia. It thus appears probable that the amount of vitamin B_{12} stored in the liver is usually more than five hundred times the daily body requirement. Under these circumstances it is understandable that, in fact, virtually all the vitamin B_{12} absorbed may be deposited in the liver and remain there for many months. The following recent observation by Pollycove, Arias and Apt[20] suggests either that cobalt^{60} is detached from an active moiety of vitamin B_{12} and deposited in the liver or that vitamin B_{12} is utilized by the liver to elaborate another substance that is utilized peripherally for erythropoiesis: after the subcutaneous injection into patients with pernicious anemia in relapse of 1 microgm. of cobalt^{60}-labeled vitamin B_{12}, there is a diagnostic reticulocyte response and a simultaneous deposition of cobalt^{60} in the liver equal to the deposition of cobalt^{60} in normal subjects or patients with pernicious anemia in remission. Since, at present, there is no direct evidence whether cobalt^{60} remains in the liver as an integral part of the vitamin B_{12} molecule, the phrase "hepatic deposition" is used here without any implication concerning the chemical status of cobalt^{60} within the liver.

The close agreement of the percentages of orally administered vitamin B_{12} absorbed as simultaneously determined by the methods of fecal elimination and hepatic deposition supports the hypothesis that the degree of hepatic deposition of cobalt^{60} corresponds to the degree of absorption of radioactive vitamin from the intestinal tract. Study of intestinal absorption of cobalt^{60}-labeled vitamin B_{12} by measurement of hepatic deposition of cobalt^{60} has the great advantage of requiring neither single nor collected specimens, and thus eliminates a most troublesome procedure and a frequent source of error. The measurements are simple, accurate and rapidly performed. This method also has the advantage of being able to quantitate the percentage of radioactive vitamin absorbed from the intestinal tract. The chief disadvantage is that a period of seven days must elapse before the measurement can be made, and a second such period is required if it is desired to determine the ratio of deposition between an oral and a parenteral dose.

All three methods of measuring absorption of vitamin B_{12} were applied to each subject to establish the degree of correlation between these methods. The data of absorption and urinary excretion on each subject are listed in Table 1 and charted in Figures 1, 2, 3 and 4. In general it is seen that intestinal absorption and urinary excretion of vitamin B_{12} are high in the normal persons and in the patients with pernicious anemia given normal human gastric juice simultaneously and low in the same patients not given the gastric juice.

These methods are especially useful in establishing

or disproving the diagnosis of Addisonian pernicious anemia in patients with achlorhydria receiving maintenance liver or vitamin B_{12} therapy in whom the diagnosis has not been adequately established, patients with achlorhydria, whose macrocytic anemia and megaloblastic bone marrow is the result of folic acid deficiency, patients with signs and symptoms of subacute combined degeneration of the spinal cord but without significantly abnormal blood or bone-marrow findings, and the rare patient in whom, because of lack of extrinsic factor, a deficiency state identical with that of Addisonian pernicious anemia, except for the presence of intrinsic factor, develops. The findings in patients of the last two groups are presented and discussed elsewhere.[21,22]

The applicability of these methods to the assay of intrinsic-factor activity is most evident. They not only are more rapid and simple than classic assay by reticulocyte response but also possess the enormous advantage of being able to employ for intrinsic-factor assay the relatively large number of patients with pernicious anemia in remission as compared with the increasingly scarce number of untreated patients with pernicious anemia in relapse.

Summary and Conclusions

Determinations of vitamin B_{12} absorption by three methods employing radioactive (cobalt^{60}-labeled) vitamin B_{12} were obtained in normal subjects and in patients with pernicious anemia in remission. The absorption data so obtained were reasonably consistent. The ranges of vitamin B_{12} absorption in normal subjects and in patients with pernicious anemia are approximately 62 to 82 per cent and 5 to 15 per cent respectively, as determined by fecal elimination and hepatic deposition of cobalt^{60}. Urinary excretion of orally administered vitamin B_{12} was 7.3 to 10.3 per cent in normal subjects and 0.6 to 1.0 per cent in patients with pernicious anemia.

The clinical diagnostic value of these methods of measuring vitamin B_{12} absorption is indicated and discussed. These methods are especially useful in establishing or disproving the diagnosis of Addisonian pernicious anemia in the relatively large group of patients with achlorhydria who are receiving maintenance liver or vitamin B_{12} therapy but whose previous course was not adequately investigated or documented.

The advantages and disadvantages of the stool, urine and hepatic methods of measuring vitamin B_{12} absorption are discussed. The urinary-excretion method is the most rapid. The hepatic-deposition method combines quantitation of absorption with great simplicity and also with freedom from specimen collections, thus eliminating a troublesome and potentially large source of error. Measurement of the hepatic deposition of cobalt^{60} is the best method so far as simplicity, ease and accuracy are concerned. By dispensing with the necessity of resorting to clinical trial of therapeutic effects in patients with pernicious anemia in relapse, these methods should bring within comparatively close grasp the determination of the nature and exact mode of action of the intrinsic factor of Castle.

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THE ANTIARRHYTHMIC ACTION OF AMBONESTYL (2-DIETHYLAMINOETHYLISONICOTINAMIDE, MC-4112)*

ALBERT SJOERDSMA, M.D., PH.D.,† HARRIET MALING, PH.D.,‡ HOUSTON W. PRATT, M.D.,§ JULIUS AXELROD, PH.D.,¶ HERBERT J. KAYDEN, M.D.,‖ AND LUTHER L. TERRY, M.D.**

BETHESDA, MARYLAND, AND WELFARE ISLAND, NEW YORK

THERE is need for effective antiarrhythmic drugs that do not have the undesirable side effects of those most widely used, quinidine and procaine amide. Although they are frequently effective in suppressing arrhythmias, the scope of application of these drugs is limited particularly by their properties of slowing cardiac conduction and lowering blood pressure. Lanzoni and Clark[1] and Clark and Etsten[2] recently introduced Ambonestyl, an analogue of procaine amide, and reported it to be as effective as procaine amide in suppressing ventricular arrhythmias induced by coronary-artery ligation in the dog. When administered intravenously to man, the drug was thought to suppress ventricular ectopic beats without significant side effects.

This report is a pharmacologic and clinical appraisal of Ambonestyl.†† The study was divided into two parts: fate of the drug in man; and action of Ambonestyl on experimental and human arrhythmias. Emphasis is given to a comparison with procaine amide, to which it is structurally related.[2]

FATE OF AMBONESTYL IN MAN

Chemical Methods

Ambonestyl was isolated from alkalinized biologic material by extraction into ethylene dichloride containing 1.5 per cent isoamyl alcohol and determined by a modification of the methyl orange procedure.[3] Ambonestyl added to plasma and urine in amounts of 5 to 50 microgm. was recovered with adequate precision (96±5 per cent). The material measured in human plasma and urine after administration of the drug was shown by the technic of comparative partition ratios[3] to have the same solubility characteristics as authentic Ambonestyl. It may be assumed, therefore, that the method measured the original drug and did not include metabolic products.

*From the Clinic of General Medicine and Experimental Therapeutics and Laboratory of Chemical Pharmacology of the National Heart Institute, National Institutes of Health, Bethesda, Maryland, and the Third (New York University) Medical Division, Goldwater Memorial Hospital, Welfare Island, New York.

†Senior investigator, National Heart Institute.

‡Investigator, Laboratory of Chemical Pharmacology, National Heart Institute.

§Assistant in medicine, New York University College of Medicine.

¶Staff member, Research Branch, National Institute of Mental Health; formerly, staff member, Laboratory of Chemical Pharmacology, National Heart Institute.

‖Assistant professor of clinical medicine, New York University College of Medicine.

**Chief, Clinic of General Medicine and Experimental Therapeutics, National Heart Institute; assistant professor of medicine, Johns Hopkins University School of Medicine.

††Kindly supplied as the hydrochloride salt by the Squibb Institute for Medical Research, New Brunswick, New Jersey.

Experimental Data

One gram of Ambonestyl was administered intravenously to man as a 5 per cent solution over a period of twenty minutes. The plasma half life in 2 subjects was four hours and fifteen minutes and five hours, indicating a rate of disappearance similar to that of procaine amide.[4] When the same amount was administered orally in capsules to the same patients, plasma levels reached a peak in one to two hours and then declined at a rate approximating that after intravenous administration. Absorption from the gastrointestinal tract is thus rapid and essentially complete. The urinary excretion of Ambonestyl after intravenous administration to 2 subjects averaged 85 per cent in forty-eight hours, indicating virtually no metabolism in the body.

Two subjects received Ambonestyl orally for six days in doses of 0.5 gm. every six hours. Plasma levels measured daily just before the noon dose ranged from 0.7 to 2.4 mg. per liter, and there was no tendency for the drug to accumulate in the body.

ACTION OF AMBONESTYL ON CARDIAC ARRHYTHMIAS

Comparison with Procaine Amide and Quinidine against Chloroform-Epinephrine-Induced Cardiac Arrhythmias in Dogs and Cats

In dogs and cats under pentobarbital anesthesia, Ambonestyl was tested for antiarrhythmic action against cardiac arrhythmias induced by epinephrine injected intravenously at the end of a brief period of chloroform administration, a modification of the procedure described by Melville[5] being followed. A standardized, multiple-dose technic of drug administration was used, and the cumulative dose of each drug producing complete protection against arrhythmias was determined in three or more animals (Table 1). The protective doses were 55 to 150 mg. per kilogram of body weight for Ambonestyl compared to 1 to 30 mg. for procaine amide and 1 to 4 mg. for quinidine. Similar experiments in cats gave values of 500 to 900 mg. for Ambonestyl, 10 to 200 mg. for procaine amide and 10 to 50 mg. for quinidine. Thus, the protective doses of Ambonestyl were much higher than those of the other two drugs.

Comparison with Procaine Amide against Cardiac Arrhythmias in Man

Thirty-six adult subjects were given Ambonestyl by intravenous infusion at a rate of 32 to 166 mg. per minute for a total dose of 0.35 to 2.7 gm. (Table

2). Sixteen were also given procaine amide intravenously on a different day at a rate of 43 to 107 mg. per minute for a total dose of 0.3 to 2.2 gm. The patients studied had arrhythmias that were consistently present from day to day except for the 2 cases of paroxysmal ventricular tachycardia and 1 case of atrial flutter with 2:1 atrioventricular block. Electrocardiograms were obtained continuously throughout the period of drug infusion, and the blood pressure and pulse rate were measured every minute. Observations were continued for an hour after completion of the infusion, the electrocardiogram, blood pressure and pulse rate being recorded every five minutes during this time. All but 1 patient (Case 3) had organic heart disease of either arteriosclerotic or rheumatic origin.

TABLE 1. *Minimal Doses* of Antiarrhythmic Drugs Producing Protection in Dogs and Cats against Chloroform-Epinephrine-Induced Ventricular Arrhythmias.*

ANIMAL	AMBONESTYL	PROCAINE AMIDE HYDROCHLORIDE	QUINIDINE SULFATE
	mg./kg.	*mg./kg.*	*mg./kg.*
Dogs (natural breathing)	55, 110, 150	1, 10, 30	1, 1, 4, 4
Cats (artificial respiration)	500†, 700, 900, 900†	10, 100, 150, 200, 200	10, 50, 50

*Each dose represents cumulative, threshold dose giving complete protection against arrhythmias in 1 animal under pentobarbital.
†Both vagus nerves cut in these cats.

Ventricular arrhythmias (Cases 1-12). Ambonestyl completely suppressed the arrhythmia in only 1 patient (Case 8) during the period of observation. This patient received the largest dose administered, 2.7 gm. In 4 other patients there was evidence of some antiarrhythmic action: complete suppression of premature ventricular contractions for five minutes in Case 3, and partial suppression for twenty to sixty minutes in Cases 7, 10 and 11. There was a marked increase in the number of contractions in 4 patients, 1 (Case 9) exhibiting a transient episode of bigeminal rhythm. Procaine amide completely suppressed the arrhythmia in 7 of 8 patients, the suppression being of only four minutes' duration in 1 patient (Case 3), who showed a similar response to Ambonestyl but subsequently reverted to a normal rhythm on quinidine, 1.2 gm. daily, given orally.

Combined ventricular and supraventricular arrhythmias (Cases 13-21). Ambonestyl had no significant effect on the supraventricular rhythm, but there was complete suppression of premature ventricular contractions in 1 patient (Case 14) with a dose of 2.4 gm. More frequent contractions were again noted in 5 patients. Procaine amide was given to 3 of these, in 1 of whom it completely suppressed the contractions. One patient reverted to a normal rhythm spontaneously.

Supraventricular arrhythmias (Cases 22-32). Neither Ambonestyl nor procaine amide (3 patients) had any detectable antiarrhythmic effect in this group. Premature ventricular contractions developed in 3 of the patients receiving Ambonestyl. Three patients were subsequently converted to normal rhythm — 2 after 0.6 and 4.0 gm. of quinidine orally in divided doses and 1 after 1.6 mg. of lanatoside C intravenously.

Atrioventricular dissociation (Cases 32-36). Ambonestyl caused premature ventricular contractions in 2 patients and ventricular tachycardia and convulsions in a third (Case 35). The fourth patient showed no response to Ambonestyl. Two patients received procaine amide without ill effect.

Other Effects

Cardiac conduction. Ambonestyl had no significant effect on cardiac conduction as measured by the PR interval and QRS segment of the electrocardiogram. However, in about a fourth of the patients there was a significant prolongation of the QT interval, which is a measure of electric systole and the relative refractory period.

The induction of premature ventricular contractions in 12 patients with normal atrioventricular conduction, and the development of premature ventricular contractions or ventricular tachycardia in 3 of the 4 patients with complete atrioventricular block indicates that the drug either has a direct excitatory effect or, more probably, in some way modifies the refractory period or conductivity allowing the discharge of ectopic foci. Three patients receiving procaine amide showed significant prolongations of PR interval, QRS segment or QT interval, as reported previously,[6] but in no case was there an induction of premature ventricular contractions.

Pulse rate and blood pressure. In this study, neither drug had a significant effect on pulse rate except through the suppression or induction of arrhythmias. Hypotension was not a problem in patients receiving Ambonestyl but necessitated cessation of procaine amide infusion in 3 patients. Nevertheless, significant falls in blood pressure were observed in several patients receiving Ambonestyl, but not of the degree seen with procaine amide.

Subjective side effects of Ambonestyl. These included sensations of drowsiness (1 patient), nausea (3 patients), dizziness (3 patients) and warmth in face and throat (4 patients). These sensations were mild and transient.

DISCUSSION

The results of this study indicate that Ambonestyl is inferior to procaine amide in the treatment of experimental and human arrhythmias. Lanzoni and Clark[1] reported suppression of ventricular arrhythmias in the dog after coronary-artery ligation with doses of Ambonestyl comparable to that of procaine amide. However, in chloroform-epinephrine-induced ventricular arrhythmias in dogs and cats (Table 1),

TABLE 2. *Effects of Ambonestyl and Procaine Amide on Human Arrhythmias.*

CASE	RHYTHM	DRUG	DOSE OF DRUG		RESPONSE*
			TOTAL (GM.)	MG./MIN.	
Ventricular arrhythmias:					
1	Ventricular tachycardia	Ambonestyl	1.5	50	0
		Procaine amide	0.6-1.0	50	++
		Ambonestyl	1.5	100	0
2	Ventricular tachycardia	Ambonestyl	1.0	50	0
		Procaine amide	0.3-0.6	50	++
3	Normal sinus rhythm & premature ventricular contractions (bigeminy)	Ambonestyl	2.0	100	+
		Procaine amide	0.6	50	+
4	Normal sinus rhythm & premature ventricular contractions	Ambonestyl	0.8	50	X
		Procaine amide	0.3	50	++
5	Normal sinus rhythm & premature ventricular contractions	Ambonestyl	1.0	50	X
		Procaine amide	1.0	50	++
6	Normal sinus rhythm & premature ventricular contractions	Ambonestyl	0.4	54	0
		Procaine amide	0.6	60	++
7	Normal sinus rhythm & premature ventricular contractions	Ambonestyl	1.2	32	+
		Procaine amide	0.4	50	++
8	Normal sinus rhythm & premature ventricular contractions	Ambonestyl	2.7	45	++
		Procaine amide	0.9	43	++
9	Normal sinus rhythm & premature ventricular contractions	Ambonestyl	1.0	50	X
10	Normal sinus rhythm & premature ventricular contractions	Ambonestyl	1.0	50	+
11	Normal sinus rhythm & premature ventricular contractions	Ambonestyl	1.0	50	+
12	Normal sinus rhythm & premature ventricular contractions	Ambonestyl	1.0	50	X
Combined ventricular & supraventricular arrhythmias:					
13	Atrial fibrillation & premature ventricular contractions	Ambonestyl	1.5	100	X
		Procaine amide	1.0	50	0
14	Atrial fibrillation & premature ventricular contractions	Ambonestyl	2.4	52	++
		Procaine amide	1.3	52	++
15	Atrial fibrillation & premature ventricular contractions	Ambonestyl	0.5	55	X
		Procaine amide	0.8	62	0
16	Atrial flutter & premature ventricular contractions	Ambonestyl	1.2	36	X
17	Atrial fibrillation & premature ventricular contractions	Ambonestyl	1.0	50	X
18	Atrial fibrillation & premature ventricular contractions	Ambonestyl	1.0	50	X
19	Atrial fibrillation & premature ventricular contractions	Ambonestyl	1.0	50	0
20	Atrial fibrillation & premature ventricular contractions	Ambonestyl	1.0	50	0
21	Atrial fibrillation & premature ventricular contractions	Ambonestyl	1.0	100	0
Supraventricular arrhythmias:					
22	Atrial fibrillation	Ambonestyl	1.0	50	X
		Procaine amide	1.0	50	0
23	Atrial fibrillation	Ambonestyl	1.0	50	0
		Procaine amide	0.5	50	0
24	Atrial fibrillation	Ambonestyl	0.5	166	X
		Procaine amide	1.4	107	0
25	Atrial fibrillation	Ambonestyl	1.0	50	X
26	Atrial fibrillation	Ambonestyl	1.0	50	0
27	Atrial fibrillation	Ambonestyl	1.0	50	0
28	Atrial flutter	Ambonestyl	1.0	50	0
29	Atrial fibrillation	Ambonestyl	1.4	46	0
30	Atrial fibrillation, with partial atrioventricular dissociation	Ambonestyl	1.0	45	0
31	Nodal rhythm	Ambonestyl	1.0	50	0
32	Nodal tachycardia	Ambonestyl	1.9	52	0
Atrioventricular dissociation:					
33	Normal sinus rhythm with atrioventricular block	Ambonestyl	0.5	50	0
		Procaine amide	0.55	68	0
34	Atrial fibrillation with atrioventricular block	Ambonestyl	0.45	30	X
		Procaine amide	2.2	50	0
35	Normal sinus rhythm with atrioventricular block	Ambonestyl	0.55	29	X
36	Normal sinus rhythm with atrioventricular block	Ambonestyl	0.35	35	X

*Responses graded as follows: 0, no effect; X, induction of premature ventricular contractions or increase in their frequency by at least 100 per cent; +, incomplete suppression of premature ventricular contractions or suppression for less than 1 hr.; ++, complete suppression of premature ventricular contractions for at least 1 hr.

the protective dose of Ambonestyl was found to be several times that of procaine amide. The protective dose in the dog under pentobarbital anesthesia was of an order that would have produced vomiting and central-nervous-system stimulation in the unanesthetized animal.[1] In man Ambonestyl appears to lack significant antiarrhythmic effect in doses comparable to procaine amide and even at lower dosage levels, Ambonestyl can induce ventricular arrhythmias. Clark and Etsten[2] reported suppression of ventricular arrhythmias by Ambonestyl in 6 patients, with no significant side effects other than transient hypotension. Their results cannot be compared with those presented here since 5 of their subjects were under anesthesia and the drug dosage was generally greater (1.5 to 3.5 gm.) than that used in this study.

Ambonestyl is another example of the fact that current methods of screening drugs for antiarrhythmic activity in animal preparations generally have not yielded results directly applicable to man. Furthermore, Winbury and Hemmer[7] have shown that no single experimental procedure can be used to predict generalized antiarrhythmic activity. Procaine amide was selected on the basis of *clinical* screening from among a number of analogues having a similar order of effectiveness on cyclopropane-epinephrine-induced arrhythmias in the dog.[8] In the absence of a reliable experimental screening procedure, greater emphasis should be placed on rapid *clinical* screening of promising agents. The agents screened clinically should have acute and possibly short-term toxicity studies in animals. Compounds that are found useful in studies in human subjects would then be given the usual vigorous chronic-toxicity studies in animals. This approach would restrict extensive chronic-toxicity studies to drugs that have demonstrable clinical usefulness and would allow a larger number of antiarrhythmic agents to be evaluated.

Summary and Conclusions

Ambonestyl is shown to be a relatively ineffective agent in the treatment of experimental and human arrhythmias. A comparison with procaine amide shows the latter agent to be definitely superior in the suppression of ventricular arrhythmias. The two drugs have similar rates of metabolism. The induction of premature ventricular contractions by Ambonestyl cautions against its further clinical use.

We are indebted to Drs. Thomas D. Stevenson and T. Phillip Waalkes, of the National Heart Institute, and to Dr. James Bruce, of the District of Columbia General Hospital, who contributed to some of these studies.

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SPECIAL ARTICLE

CHEMICAL CONTROL OF PULMONARY VENTILATION*

I. The Physiology of the Chemoreceptors

Hans Winterstein, M.D.†

Istanbul, Turkey

IN my first lecture I shall deal with chemoreceptors —that is, the nervous structures that control the lungs according to the chemical composition of the blood. Their discovery by Heymans and Bouckaert[1] represents one of the greatest revolutions in the physiology of respiration. It is not as if the idea of a control of respiratory movements by peripheral nerves were something entirely new, since Hering and Breuer,[2] nearly a hundred years ago, discovered the so-called self-regulation of respiration by proprioceptor reflexes. It seems that sixty years ago even the thought had been put forward by Speck[3] that the influence of carbon dioxide on pulmonary ventilation had its origin in some of the lung vessels themselves. But so many experiments seemed to prove the direct central effect of excess carbon dioxide and lack of oxygen that nobody gave consideration to suggestions not founded on experimental evidence.

At the beginning of this century Frédéricq,[4] the father of the present professor of physiology in Liége, performed his famous experiment of the *circulation croisée* — that is, crossed circulation. He crosscon-

*The first Edward K. Dunham Lecture, delivered at Harvard Medical School, Boston, October 14, 1955.

†Research professor of physiology, Institute of Physiology, University of Istanbul.

nected both the carotid arteries and the jugular veins of two dogs, so that the head and therefore the brain of each dog received the greater part of its blood supply from the other dog. If asphyxia was produced in one of the dogs — for example, by clamping of the trachea — hyperpnea was observed in the other. Similarly, hyperventilation in one dog caused diminution of ventilation of the other, even to the point of complete apnea. This seemed a clear and direct proof of the cerebral origin of the influence of the blood.

But Heymans, the famous pharmacologist of Liége, and his father[5] modified Frédéricq's experiment in the most ingenious way, shown on the right side of Figure 1. They set up the same crossed circulation, but in dog B they separated all connections between the head and the body with the single exception of the two vagus nerves. If in the body of dog B a state of dyspnea was produced by reduction of the artificial

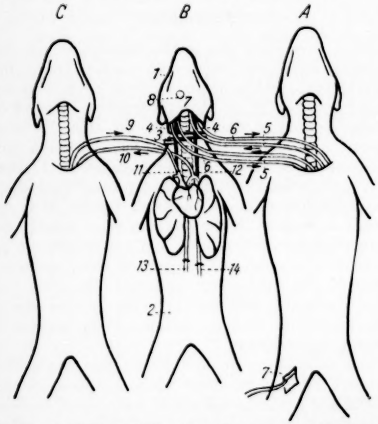

FIGURE 1. *Isolated Head (after Heymans and Heymans[5]).*

respiration, by the addition of carbon dioxide to the inspired air or by lowering its oxygen content, the larynx of the isolated head showed hyperpneic movements although the blood of its asphyxiated body did not reach the head at all. Therefore, this phenomenon could only be a question of a reflex initiated by an excitation of the vagus nerves.

The authors observed something else. They found that if the blood pressure in the body of dog B was increased — for example, by the injection of epinephrine — in the head of this animal, connected as it was only by the vagus nerves to its own body and receiving its blood supply exclusively from dog A, they saw a reduction of respiratory movements. Conversely, a reduction of blood pressure by hemorrhage in the body of dog B increased the throat movements in its own head.

And here I may recount an anecdote of my youth, after I had started to study medicine. Immediately after my first examination in anatomy and physiology I decided to become a physiologist. I went to the well known physiologist, Verworn, and worked in his laboratory. I was doing experiments on rabbits, during which I clamped the aortic arch (I no longer remember for what reason). I recollect noticing that respiratory movements were distinctly reduced, and were restored when I unclamped the aorta. I obtained this result several times but not regularly and did not follow it up. So, thirty years before Heymans and Bouckaert[6] I had discovered the so-called pressure reflex — that is, a reflex action on pulmonary ventilation produced, at least apparently, by blood-pressure changes; unluckily, I did not understand the importance of it. When I mention a reflex produced by pressure in a lecture on chemoreceptors, I do so for the following reasons: in the first place, because the discovery of pressoreceptor and chemoreceptor reflexes are intimately connected with each other, and secondly because modern research has shown that the whole pressor effects on respiration may be produced by the fact that pressure variations (changing blood velocity) may influence the effective concentrations of oxygen and carbon dioxide and in this way produce a *chemoreflex*.

The same effect as that produced by direct interference with the body of dog B can be observed when the heart and aortic arch are included in the circulation of a third animal, dog C, as shown in Figure 1.

It is not necessary to go into the details of the blood-vessel connections. In effect, the isolated head of dog B, receiving its blood supply from dog A only, is connected by the vagus nerves to a heart-lung preparation, which, however, receives its blood supply from dog C. According to the degree to which this blood is oxygenated or asphyxiated the respiratory movements in the isolated head decrease or increase. This proves factually that it is the chemical composition of the blood that causes the excitation, reflexly conducted by the vagus nerves to the isolated head of dog B.

The problem now to be decided is whether the seat of this excitation is the heart and aortic arch or the lungs. By a clever arrangement of the circulatory connections the Heymanses succeeded also in solving this problem in an incontestable fashion. If the blood of dog C was allowed to flow only through the heart, but not the lungs, of dog B, none of the effects described changed. If, on the other hand, an isolated lung circulation was set up, although the mechanical Hering–Breuer reflexes were preserved, the chemical composition of the blood flowing through the lungs had no effect whatever. Consequently, something entirely new had been discovered — namely, a chemosensitivity in the region of heart and aorta.

In the same way as in the cardiac region of the

aorta, so also in the so-called carotid sinus at the fork of the common carotid artery, it was first the *mechanical* effects on respiratory movements that attracted attention. The reflex regulation of blood pressure by way of the carotid nerve had long ago been discovered by Hering. Heymans and his collaborators[7] studied the effects on the organism of artificial perfusion of the carotid sinus. They found that an increase of pressure produced reflex apnea, and a decrease of pressure, a reflex hyperpnea, both of which disappeared after denervation of the sinus. A few years later followed the epoch-making discovery that not only the pressure but also the chemical composition of the fluid passing through the sinus affected the magnitude of respiration. Blood rich in carbon dioxide caused an increase, and blood poor in carbon dioxide a decrease in lung ventilation. Similar effects could be produced by variation of the pH of the perfusion fluid. These effects also disappeared when the sinus nerve was cut. Far more important still was the observation that these kinds of effects could be obtained by changes of the composition of the blood happening in the living organism itself.[7] This was shown by the ingenious method of perfusion of the isolated head by a donor dog, modified as shown in Figure 2.

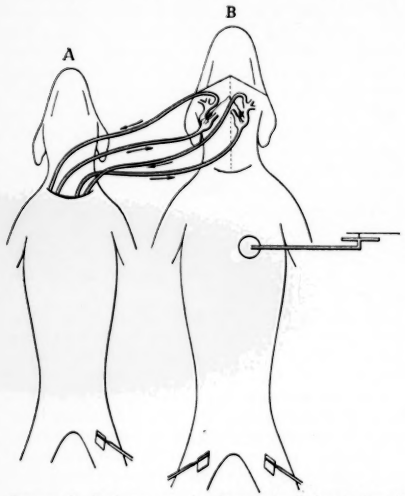

FIGURE 2. *Perfusion of the Vascularly Isolated Carotid Sinuses (after Heymans, Bouckaert and Dautrebande[7]).*

The cardiac stumps of the carotid arteries of donor dog A were connected again with the cranial ends of the carotid arteries of the isolated head of dog B, so that both its carotid sinuses obtained their blood from dog A. All the outlets of the carotid sinuses were ligated, except one lingual artery, which was connected with the cardial stump of the jugular vein of dog A, so that the blood from the carotid sinuses of dog B was returned into the circulation of dog A. In this way both carotid sinuses of dog B were brought into the circulation of dog A and were functionally connected with the head of the former only by its carotid nerves. But, as before, the throat movements of dog B reacted in accordance with the chemical composition of the blood of dog A. Again, asphyxia of dog A produced hyperpnea, and hyperventilation apnea, in dog B. Similar hyperpnea was induced in dog B if dog A was made to breathe air containing more carbon dioxide or less oxygen than normal. Therefore, the respiratory movements of the head of dog B must have been controlled by reflex impulses originating in the carbon dioxide and oxygen pressures in the carotid sinuses and conducted through the carotid nerves to the respiratory centers.

MORPHOLOGY

As I have said, the nerves responsible for the chemical respiratory reflexes are of two kinds: the carotid nerve, or Hering nerve, whose fibers originate in the sinus region; and the aortic nerve, or nerve of Cyon, originating from the aortic arch. I have already mentioned that long before Heymans and Heymans discovered the chemosensitivity of these nerves, their sensitivity to blood pressure and their regulating effects on it were well known. Any increase in pressure in the aortic arch or the carotid sinus leads to a reflex drop, and any diminution in pressure to a reflex rise, in general blood pressure, which in this way is kept constant. Therefore, one must distinguish between the pressoreceptor effect, now known for so long, and the newly discovered chemoreceptor effects.

The outstanding Spanish histologist, de Castro,[8] put forward the hypothesis that the fibers of the carotid and aortic nerves, which react to the pressure on one hand and to chemical stimulation on the other hand, are also to be distinguished anatomically from each other. In this case the pressoreceptors and the chemoreceptors would be entirely separate and distinct nervous structures. Heymans and his collaborators were again the first to demonstrate physiologically the truth of this supposition. It is impossible to go into the details of all the well planned experiments set up for this purpose. I should like to confine myself to a particularly brilliant example carried out by Heymans's collaborators, Bouckaert and Pannier.[9] Before explaining it I must introduce the fact that, as Heymans and his collaborators have shown, there are a number of substances whose introduction into the blood stream affects the respiration solely by way of chemoreceptors. Among these substances is sodium sulfide, which for this reason can be used as an index of chemoreceptor excitation. Figure 3 shows diagrammatically at A the arrange-

ment of the blood vessels of the carotid sinus. The external carotid artery (1), the occipital artery (2) and the internal carotid artery (3) are ligated. If the common carotid artery is now clamped there is a drop of pressure in the sinus and a rise in the general blood pressure, as shown in the record below A indicated by a-b. If sodium sulfide is injected into the common carotid nerve there is a strong increase in respiration in record R at c.

Now in diagram B by means of fine scissors all nerve fibers along the line 6 - 6′ are severed, but the peculiar structure outside the sinus remains untouched. If the former procedure is now repeated, clamping the common carotid has no effect at all, as shown below B. This means the pressoreceptors have been put out of action. Injection of sodium sulfide gives the same effect as before, at c, showing that the chemoreceptors have been preserved intact. If the sinus nerve is also cut, as shown in diagram C at the line 7 - 7′, this effect also vanishes.

Figure 4 shows the crucial experiment, in which the external carotid artery (3) is again ligated, but this time higher up at 1 after the lingual artery (2) has branched off, which therefore retains its blood supply. The occipital (5) and internal carotid (6) arteries are ligated as before, and for the time being

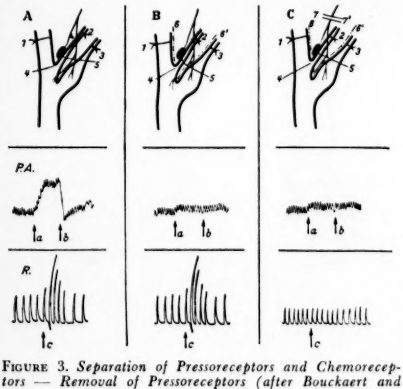

FIGURE 3. *Separation of Pressoreceptors and Chemoreceptors — Removal of Pressoreceptors (after Bouckaert and Pannier[3]).*

both pressoreflexes and chemoreflexes can be obtained as in the former experiment. If the pharyngeal artery (4) and for the second time the occipital artery (5) are ligated at 9, this time below the peculiar structure already mentioned, so that its blood supply is completely cut off, although the pressoreflexes — as shown in the record — are preserved just as before, the injection of sodium sulfide remains without any effect.

These experiments show beyond any question that the chemoreceptor fibers have their origin in this structure situated between the two carotid arteries whereas the pressoreceptor fibers originate from the walls of the sinus itself. There is an analogous situation in the aortic region, where it can also be demonstrated that the chemoreceptor fibers originate from similar structures, although more scattered than in the sinus and situated chiefly beneath the aortic arch, between it and the pulmonary artery in the so-called Pemitschka ganglion. The whole arrangement is diagrammatically shown in Figure 5.

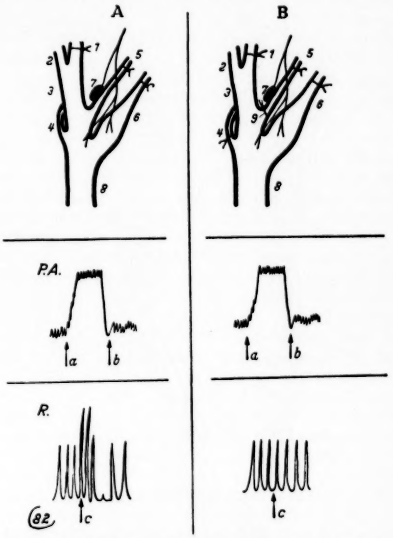

FIGURE 4. *Separation of Pressoreceptors and Chemoreceptors — Removal of Chemoreceptors (after Bouckaert and Pannier[3]).*

Figure 6 shows a scheme of the large epithelioid cells of these structures and the sensitive nerve fibers originating from them. They are surrounded by a rich capillary network to which they owe the anatomic name of *glomus* (meaning "knot"). In English they are usually referred to as "bodies" and called the "carotid bodies" and the "aortic bodies." I prefer the Latin name because of its international connotation and because it allows one to use the adjective "glomerogenic" for the impulses starting from both of them. These, indeed, are the structures that send their drive to the respiratory center partly through the glossopharyngeal and partly through the vagus nerve and their importance has proved to be surprisingly great.

FUNCTION

Between wide limits the organism adapts the magnitude of its respiratory movements according to

its need. Now comes the much disputed question not yet completely solved about the relative parts played in this adaptation by the chemoreceptor drive on the one hand and by the direct central drive on the other. When Heymans and his collaborators first discovered the control of respiration by chemoreceptors they believed that the predominance of the center would be dethroned, and they emphasized the fact that the reflex sensitivity to carbon dioxide and oxygen lack was greater than that of the center.

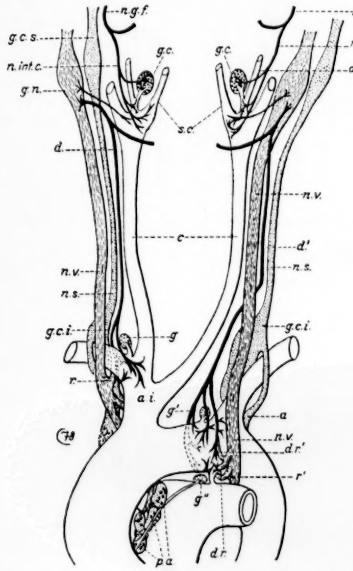

FIGURE 5. *Anatomy of Chemoreceptors (after de Castro[9]).*

Until now I have used exclusively the term "carbonic acid." In my third lecture I shall try to prove that all the effects on pulmonary ventilation generally attributed to this substance are really not specific effects of carbon dioxide itself but rather of dissociated carbonic acid — that is, of hydrogen ions. But for the time being one may continue to speak about carbon dioxide.

A wide variety of experiments has proved that under normal conditions the carotid chemoreceptors play a considerable part in the control of respiration. If they are removed this operation is alone sufficient to cause an increase in the alveolar carbon dioxide pressure, showing that the ventilation has decreased. This is still more apparent when a little carbon dioxide is added to the inspired air. The increase of respiration produced in this way is noticeably greater in normal animals then after removal of the chemoreceptors.

There is a more direct way to demonstrate activity in nerve, and that is by showing the action potentials accompanying it. These potentials too were first demonstrated in the sinus nerve by Heymans and Rijlant[10] and received special attention from the Swedish workers Euler, Liljestrand and Zotterman.[11] Using anesthetized cats, they were able to show that the carotid nerves were in a continuous state of tonic excitation even under normal conditions. This was also true when any effect of insufficient oxygen pressure was excluded by allowing the animals to breath pure oxygen. Only when artificial respiration had so far increased the pulmonary ventilation that the value of alveolar oxygen pressure had fallen from its normal level of more than 35 mm. to less than 30 mm. did action currents disappear from the carotid nerve. This is clear and indisputable proof that the chemoreceptors under normal conditions play a part in the control of respiration.

A considerable technical improvement was the introduction of the cold-block method by which the activity of a nerve can be stopped without operative damage. The nerve is placed on a small metal tube, through which alcohol of any desired temperature can be circulated. In a few seconds conduction in

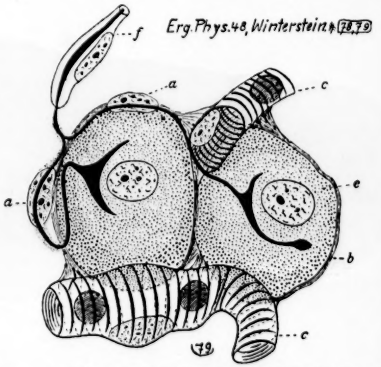

FIGURE 6. *Scheme of Glomus Synapsis (after de Castro[9]).*

the nerve can be abolished by low temperature. With this method it was also possible to show that blocking of the carotid nerves produced a reduction of ventilation, which therefore under normal conditions can be maintained at its usual level only with a contribution from the chemoreceptor drive.[12,13]

As is clear from what I have already said, the chemoreceptors play an important part in the control of respiration by carbon dioxide, but, moreover, all workers in this field agree that their importance concerning the influence of oxygen pressure on

pulmonary ventilation is far greater. The question under discussion is not whether oxygen lack is also effective by way of the chemoreceptors, but whether there would be any direct central effect without them. A large number of experiments suggest that lack of oxygen has its well known excitatory effect on respiration exclusively through the chemoreceptors. Whereas a reduction of the oxygen content of the inspired air to about two thirds the normal value leads, both in man and in the usual laboratory animals, to an immediate increase of respiratory movements, one sees no such increase after removal of the chemoreceptors. Indeed, with advancing hypoxia, a *decrease* of ventilation that soon leads to death is observed under these conditions.

Most of these experiments were, as usual, carried out on anesthetized animals. Thus, the suspicion arose that the anesthesia itself might in some way have contributed to this effect. The first experiments in which such an action was demonstrated were carried out here by Beecher and Moyer,[14] using light hexobarbital (Evipal) and thiopental (Pentothal) anesthesia. Although here, too, as opposed to the effect of oxygen lack on normal animals, the first reaction was always a reduction of respiration, it was followed a few minutes later by excitation phenomena. These, however, were different from normal in that they were irregular, periodic and sometimes accompanied by motor spasms. Increase of the depth of anesthesia caused all these phenomena to disappear, and only the depressive effects remained.

Experiments on unanesthetized animals met with great difficulties. It is relatively easy to extirpate or denervate the carotid sinuses, but extremely difficult to denervate the aorta. The only absolutely certain way is to cut the vagus nerves in the neck region. But this cannot be done if the animals are to continue living. A satisfactory result can only be achieved through a difficult intrathoracic operation in which the vital fibers of the vagus nerves are left undamaged. However, such dogs were prepared by Watt and his collaborators,[15] and on them fundamental observations were made by Chambers et al.,[16,17] who confirmed the findings of Beecher and Moyer[14] that after a period of depression lasting several minutes, which clearly distinguished these animals from those with functioning chemoreceptors, a temporary period of excitation supervened.

Now, as for carbon dioxide, there is the question of the influence that the oxygen pressure exercises by means of the chemoreceptors, *under normal conditions,* when no oxygen lack is present. In effect, do the chemoreceptors play a part or not? It has already been shown that without the chemoreceptors the organism is not capable of maintaining its normal alveolar carbon dioxide pressure. What happens if the oxygen pressure is increased above the normal level? If the chemoreceptor activity were independent of oxygen pressure under normal conditions one would expect such an increase to remain without effect.

It seems to me that the experiments of Loeschcke, using not pure oxygen, which may have some noxious effect, but the undoubtedly harmless oxygen content of 32 per cent, have solved the problem conclusively for human subjects. He was able to show in a statistically significant way that under these conditions there is a reduction of pulmonary ventilation. Loeschcke calculated that the chemoreceptors must be responsible for 12 to 14 per cent of respiratory movement as far as oxygen insufficiency is concerned.

It can be concluded, from the chemoreceptor point of view, that there is normally a state of slight excess of carbon dioxide pressure and a slight lack of oxygen pressure that keep these sensory organs in permanent tonic excitation. To remove this excitation the alveolar carbon dioxide pressure would have to be 30 instead of 40 mm. and the oxygen content of the inspired air about .30 per cent instead of 21 per cent.

Thus, it can be seen that, even under normal conditions, the control of respiration is due partly to the central drive and partly to the chemoreceptor drive. Now comes the interesting and important question of the part played by these two kinds of drives under the different conditions to which the organism must adapt itself. On human subjects such studies can only be carried out in a limited way, because they necessitate a comparison of how the pulmonary ventilation behaves with and without chemoreceptors. Elimination of their chief function — namely, sensitivity to lack of oxygen — can only be achieved by elimination of the oxygen lack, which, of course, is exactly the factor one wishes to investigate. The most that can be done is to correct an oxygen lack by sudden inspiration of air with a high oxygen content and to see what happens. If nothing happened it would mean that the chemoreceptors played no part in the control of respiration. If, on the contrary, the whole previous excess of respiration disappeared completely, it would mean that this excess was 100 per cent due to a glomerogenic drive. I shall return to this subject in my second lecture in discussing the acclimatization to high altitudes.

However, in experiments on animals the excellent method of blocking the nerve by cold, applied to the sinus nerve of an animal with all the other chemoreceptors removed, makes possible the elimination of the glomerogenic impulse at will and for as long as desired. The behavior of respiration when this is done permits one to estimate the part played by central and by peripheral drive. It was by using this method that Gesell and his collaborators[13] in Ann Arbor and the Swedish worker Bjurstedt[18] carried out their fundamental researches with some surprising results. It should be said immediately that, according to

them, the part of the chemoreceptor drive can vary between 0 and 100 per cent according to conditions. The only disadvantage of these experiments, compared with those on human subjects, is again that they were carried out on anesthetized animals and therefore can only be accepted with reserve as valid for the unanesthetized organism.

It is well known that even small quantities of carbon dioxide effect a considerable increase in respiration. Furthermore, as already discussed in some detail, carbon dioxide produces an excitation of the chemoreceptors under normal conditions. Therefore, one might think that the greater the carbon dioxide concentration of the inspired air, the greater the part played in respiration by the chemoreceptor drive. Gesell et al.[13] investigated this problem using the technic of cold blocking of the sinus nerve, and found exactly the opposite: the greater the concentration, the less the effect on respiration of temporary blocking of the sinus nerve. When the concentration in the inspired air reaches 5 to 6 per cent the chemoreceptors have no effect at all, and respiration is controlled 100 per cent by the central drive. Carbon dioxide pressure and hydrogen ion concentration, and therefore their effects as well, go hand in hand under normal conditions. The Swedish researchers Bjurstedt[18] and Gernandt[19] studied the effect on respiration of cold blocking of the sinus nerve at different blood pH. Gesell's results were completely confirmed. The greater the acidity of the blood — or, more correctly, the less its alkalinity — the less the effect of sinus-nerve block, and the more alkaline the blood, the greater the effect. Above a certain hydrogen ion concentration, blocking had no effect at all — that is, control of respiration was exclusively central. On the contrary, below a certain hydrogen ion concentration cold block produced complete apnea, showing that control by the chemoreceptors was 100 per cent. This is a remarkable phenomenon and even today has not been completely explained.

As mentioned above, artificial perfusion of the isolated sinus showed that acid reaction solutions, or those containing carbon dioxide, produce excitation of the glomeric apparatus. How is it possible, therefore, that the researches uniformly demonstrated exactly the opposite, in the sense that the greater the alkalinity the greater the effect, and the less the alkalinity the less the effect? It seems to me that there are two possibilities to explain this apparent contradiction: one is based on the Bohr effect, and the other on the Weber law. The former consists in the fact, discovered by the Danish physiologist, Bohr, that the oxygen capacity of the hemoglobin depends not only on the oxygen pressure but also on the carbon dioxide pressure or, what really amounts to the same thing, on the pH of the blood. The more alkaline the blood, the greater the quantity of oxygen, and the less alkaline, the smaller the quantity of oxygen absorbed by the blood at the same oxygen pressure. If the pH of the blood containing a certain quantity of oxygen is shifted toward the acid side, the oxygen pressure will increase, even though the quantity remains the same. Toward the alkaline side the opposite is true. It is almost like the rising and sinking of water when one presses or releases the sides of an elastic vessel.

To use these facts to help explain the problem under discussion one must first know on what the excitation of the chemoreceptors exactly depends. Many experiments have shown without question that, as far as oxygen is concerned, the determining factor for excitation is oxygen pressure but not saturation. A most striking example of this is an experiment on cats carried out by Duke and his collaborators.[20] Hemoglobin has a hundred and fifty times more affinity for carbon monoxide than for oxygen. So that if an animal is made to breathe air containing a little carbon monoxide, a large part of the hemoglobin will be bound to it. However, the oxygen pressure is not changed, because the blood, now as before, is in equilibrium with the alveolar air. Now, the authors led off the action potentials from the sinus nerve that directly reflect its state of excitation. By adding carbon monoxide to the inspired air so that the oxygen content of the blood was reduced by 70 to 80 and sometimes even 90 per cent, they found no change in the state of excitation of the chemoreceptors as long as the oxygen pressure remained the same.

And now one is in a position to understand what happens when the pH of the blood is shifted toward the acid side. Although the oxygen *content* of the blood is not changed, the oxygen *pressure* will be increased. Therefore, there will be less excitation in the chemoreceptors, with consequent decrease of pulmonary ventilation. Bjurstedt had taken this factor into account but, as I found by calculation, had underestimated in his experiments the magnitude of the Bohr effect. However, it does not seem to me probable that an explanation on these lines is sufficient to account for all cases. I am accordingly driven to seek another possibility.

As stated above, there are two chief methods of estimating chemoreceptor activity: measurement of the action potentials; and elimination of the activity by the use of the cold block. But these two methods are not really measuring the same thing. The action potentials give a true picture of the *state of excitation* of the chemoreceptors and therefore of the magnitude of the glomerogenic drive. By contrast the cold block indicates the magnitude of the *effect* on the centers of this drive. It is not at all necessary that these two should be proportional. Weber's law concerning sense physiology states that the least perceptible increase of stimulus bears a constant relation to the magnitude of the present state of excitation. This means that the magnitude of an incoming stimulus, if it is to be effective, must be in proportion to the excitation of the organ in question. Conversely, the effect of a

stimulus of specific magnitude will be less in proportion to the previous excitation of the organ. Something resembling the Weber law can be applied to the respiratory center, whose degree of excitation goes hand in hand with the hydrogen ion concentration. Then one can see why the same or perhaps even a stronger glomerogenic drive will have less effect if the hydrogen ion concentration is increased — and no effect at all above a certain level. On the contrary a decrease of the state of excitation in the respiratory center, caused by a shift of the pH of the blood toward the alkaline side, will endow the glomerogenic drive with increased effectiveness.

This is a hypothesis that would be quite accessible to experimental investigation. It would only be necessary, on the one hand, to lead off the action potentials of the sinus nerve that would show the magnitude of the glomerogenic drive and, on the other hand, to apply a cold block to the sinus nerve of the other side to measure the *effect* of this drive. The results of this experiment, which as far as I know has never been performed, would show whether this hypothesis of a disagreement between the magnitude of the chemoreceptor drive and that of its effect is correct.

Summary

In the organism there are two tasks whose solution is of the greatest importance. In the first place, the acid-base equilibrium must be kept constant; secondly, the oxygen supply must be adequate. The chemoreceptors provide the finer adjustment of both. But the second task is immediately vital, in the sense that an insufficient oxygen supply leads directly to death. One finds, therefore, that nature has endowed these peripheral sensory organs with special sensitivity to changes of oxygen pressure, so that they are able to compensate for any disturbance, long before the centers have been affected. However, this compensation is, as will be pointed out in a succeeding lecture, connected with alterations in the acid-base equilibrium. This fact results in an extraordinarily complicated interaction of peripheral and central regulatory mechanisms, to be discussed in my second lecture.

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MEDICAL PROGRESS

DIABETES MELLITUS (Concluded)

Samuel B. Beaser, M.D.*

BOSTON

Diagnosis

Early diagnosis of diabetes can be achieved only by a full realization of the length of the silent biochemical phase of this disease.[126] Also, its dynamic and fluctuating character even at this early stage must be recognized. The most frequent method of early detection is urinalysis. The recent appearance of two very convenient test-paper methods will be helpful for this purpose. Both use paper impregnated with glucose oxidase and peroxidase that produce nascent oxygen when in contact with beta glucose. Testape† incorporates a dye that turns shades of color from yellow to blue, paralleling the present semiquantitative methods. Clinistix‡ incorporates orthotolidine,

*Clinical associate in medicine, Harvard Medical School; head, Abraham Rudy Diabetes Clinic of the Medical Service, Beth Israel Hospital.

†Available from Eli Lilly and Company, Indianapolis, Indiana.
‡Available from Ames Company, Incorporated, Elkhart, Indiana.

which when oxidized is a deep blue. This is not quantitative and simply screens for glycosuria. The enzyme system is more sensitive than present methods but is more specific and less likely to give false-positive reactions. The fact that alpha glucose is the form excreted and must first change to beta glucose for detection (only after standing in the bladder or outside) should make it less sensitive.

Although the oral glucose tolerance test is still the simplest method of testing for diabetes, it measures other variables.[107] By the use of a rapid intravenous injection of glucose a mathematical glucose utilization constant can be calculated.[127,128] This is quicker (one hour), free of variables due to absorption and independent of the height of the initial fasting blood sugar. It can distinguish between mild diabetes and nondiabetic conditions. Its disadvantages are largely technical such as multiple venipunctures. Further use of blood phosphate measurements ancillary to the glucose tolerance test has indicated that it is of value only with the *intravenous* glucose tolerance test and cannot be applied to individual cases.[129,130]

A new and valuable approach is that of combining steroid stress with the glucose load. A single dose of cortisone (200 mg.) orally or ACTH (100 mg.) subcutaneously given before the test worsens the oral glucose tolerance test. This has been applied to diabetes detection. In diabetic patients and in many siblings of diabetic persons (over fifty years of age) ACTH worsens the glucose tolerance test, but not in control patients.[131] By this method, persistence of impaired glucose tolerance can be demonstrated in some diabetic patients who are in an apparent remission.[132]

A flat glucose tolerance curve occurs in many normal people and has been difficult to explain. By simultaneously performed fluoroscopic x-ray examination of the stomach in 26 such persons it has been shown not to be due to delayed emptying time.[133] The best explanation at present is decreased speed of absorption. In two thirds of the patients studied glucose tolerance reverted to normal on subsequent repetition.

Clinical Diabetes

Diabetes in childhood presents many important theoretical and clinical problems. The characteristic dynamic course of remission and then reactivation has been delineated by Hartmann et al.[124] and Kelly, Ras and Jackson.[125] This presents the challenge to prevent the inevitable outcome associated with low pancreatic-islet function. Free diet and hyperglycemia in childhood lead to decreased growth.[134] Nutritionally adequate and attractive diets can be planned that are compatible with both normoglycemia[135] and growth. Yet, in clinical practice, diets prescribed for diabetic children are frequently inadequate in total calories.[136] Regardless of dietary prescription, however, there is a tendency to voluntary increases in diet on the part of the patients, frequently with nutritionally inadequate sweets and apparently increased insulin needs. There is a close mathematical relation between weight and actual insulin requirement throughout childhood.[125] As a result, with the onset of growth, there is a very decided increase in insulin requirement. The age at onset does not influence insulin requirement.[125] Fructose and sucrose have been substituted for glucose in a planned clinical experiment in childhood, with no effect on insulin requirements.[124]

The interaction of personality problems of childhood and an intricate disease such as diabetes poses almost insuperable difficulties. That the diabetes itself is not the cause of these personality aberrations is well illustrated in a recent detailed review of 10 such cases.[137]

The problem of education and re-education of the adult as well as the juvenile diabetic patient in the proper attitude toward his disease has not been successfully met. The factors responsible have been recently analyzed, and it has been proposed that patient education about the disease be included as an integral part of every hospitalized diabetic person.[138] This could be included among the minimum standards of hospital care.

Therapy

Insulin

The American experience with lente insulin[139-142] confirms the English opinion[143] that it is similar in action to that of NPH. It can also be mixed with American-made crystalline insulin in almost any ratio desired. The hope that it might be less allergenic has not been realized.[139,140] Ultralente and semilente insulins are now being given clinical trial. If ultralente proves equivalent to protamine zinc insulin, lente and ultralente insulin may well eventually be substituted for their more complex equivalents.

Patients with brittle diabetes still present problems with any type of insulin. The use of long-acting insulins has created the problem of the nocturnal reaction, which not only may be missed but also, because of counterregulatory factors, can cause a hyperglycemic rebound, with morning glycosuria. Thus, the patient may be given additional insulin in error if this mechanism is not considered.[144] Close study of a group of patients with brittle diabetes revealed 4 juvenile patients who also had abdominal distention and hepatomegaly.[145] Liver biopsy showed excess glycogen; yet glucagon, paradoxically, caused less than normal hyperglycemia. Metabolic study of cases of severe diabetes in which insulin was reduced or withdrawn seemed to point up a metabolic difference between the stable and the labile disease. Glycosuria developed in both, but the patient with labile diabetes

also had a prompt and significant negative nitrogen balance.[146]

In insulin allergy (without resistance) of a severe degree, desensitization can be carried out safely under the protective influence of oral cortisone therapy.[147] The nature of the local skin reaction to insulin is still subject to contradictory interpretation. On the one hand, it has been regarded as merely a mechanical result of too superficial injection (by slant injection into the folded skin) and not to skin sensitivity.[148] On the other hand, Paley[149] has found positive allergenic skin tests to insulin in such patients, even to the newer lente insulins. However, he could not concentrate the dermal-reacting factor.

Oral Hypoglycemic Sulfonamide Compounds

Oral sulfonamide compounds with remarkable hypoglycemic qualities and without significant toxicity have recently been introduced. Originally discovered as 2254 RP by Loubatières (and Janbon)[150,151] in 1942 and more recently modified in Germany as BZ55 (Carbutamide*) and D860 (Orinase†), they are now being used extensively in the United States.[63,152-155]

After oral administration, the blood sulfonamide level rises promptly whereas the blood sugar drops to its nadir at three hours and reverts to normal in six hours. Because of slow excretion, cumulative effect and successive potentiation of repeated doses, the administration of these drugs day after day results in ameliorative effects on experimental and human diabetes. All three compounds behave similarly. They have a minimum effective dose and a maximum beneficial dose. The effect is all or none, unlike that of insulin. There is a wide margin of safety, the severely toxic dose being twenty times the minimum effective dose.[153]

Their action requires the presence of relatively intact islet tissue of the pancreas. The probable mechanism is the stimulation of the islet cells and in part a reduction in action of hepatic "insulinase."[63] It is not due to the inhibition of glucagon.[155] Their lack of action in severe diabetes has been explained on the grounds of "insulin lack." More optimistically, it has been suggested that the lack of activity in some severe cases may be due to a difference in the metabolism of the sulfonamides in such patients rather than in its fundamental action.[156]

Several thousand diabetic patients have up to now been treated with these drugs in Europe and the United States. They are administered as 0.5-gm. tablets, 2 to 4 per day in one or two doses after a priming period of a day or two with larger doses (6 tablets). They are effective in 50 to 80 per cent of cases, depending on the selection of cases and the index of therapeutic success accepted. Older patients with disease and insulin therapy of shorter duration are said to react most favorably. Patients with severe disease or juvenile diabetic patients show the least effect, although the tablets could be used to reduce their insulin needs. The exceptions are so numerous, however, that any diabetic patient could be offered the therapy — in the most severe cases, however, with hospitalization. The evidence for permanent benefit to the diabetes, human or experimental, seems doubtful at present. Toxicity has been minimal, with mild skin rashes in 1 per cent of cases and no evidence of serious liver, kidney or hemopoietic effect.[154] There has been no development of resistance to the drug to date.

*Available from Eli Lilly and Company, Indianapolis, Indiana.
†Available from the Upjohn Company, Kalamazoo, Michigan.

Pregnancy and Diabetes

More detailed study has been made of the influence of pregnancy on pre-existing diabetes.[157,158] In the second or third month there is a tendency to improvement, with insulin reactions but little threat to fetal life. At the seventh to the ninth month, there is a tendency to worsening with the occurrence of spontaneous acidosis of sudden onset, rapid progress and deceptively low blood sugar levels (for acidosis). This lasts one or two months and is a threat to the fetus. The over-all average increase in insulin dosage is about 75 per cent although some patients show none. There is usually little change in the last six weeks. Post partum, there is usually a reversion to the antepartum status[158,159] in spite of reports of exceptional cases.[160] Hoet's[160] view is that pregnancy is not merely a reversible strain on the normal carbohydrate metabolism, but that in the susceptible patient it may cause permanent diabetes immediately or later ("metagestational" diabetes). This has yet to be proved statistically.[115]

Nausea in the early months and the lowered renal threshold of pregnancy add to the difficulties of diabetic regulation. Yet good diabetic regulation is considered vital to a favorable outcome. Frequent follow-up examinations at intervals of one or two weeks,[161,163] acetone testing by the patient, and reliance on the blood sugar rather than urinary sugar are necessary. To give complete co-operation, the patients must be properly apprised of the differences in regulation technics during pregnancy. The obstetrician can be helpful in this educational task.

Further experience regarding the method of handling the pregnancy of the diabetic patient supports most of the opinions expressed in the previous review.[3] Although the route of delivery is not important,[164,165] good obstetric judgment and the early timing of the delivery at the thirty-sixth to the thirty-eighth week are vital.[161,162,164,165] Deaths before that time occur in fetuses whose condition is actually not compatible with extrauterine life.[164] Calcification in the distal epiphysis of the femur that occurs at the thirty-fifth week can be accurately determined by x-ray study in 90 per cent of cases, with no

false-positive results, and can be useful to time delivery.[166] Hormone therapy contributes nothing clinically.[162,164,167] Restudy of hormone excretion in diabetic pregnancies shows less abnormality than originally reported[165] and less effect of hormone therapy upon it. This is more compatible with the view that such abnormalities are a result, not a cause, of the placental failure.

Although diabetes with higher insulin requirements may be associated with a higher fetal mortality than milder cases,[161] even the mildest diabetes (that discovered by glucose tolerance test during that pregnancy) increases fetal mortality significantly. Implicit in this is prompt diagnosis, by means of a glucose tolerance test, in all cases of glycosuria of pregnancy, with a repetition in subsequent trimesters when the value is normal.[160] Further experience is necessary to decide whether the pregnancy of these patients should be terminated early.

Good diabetic and obstetric care based on the principles mentioned above has resulted in a progressively decreasing fetal mortality, down to 10 to 14 per cent, in diabetes. Some advocate hospitalization in the last three to eight weeks of pregnancy.[159]

The infant of a diabetic mother is clearly larger than normal[168] and subject to an increased hazard of death from respiratory difficulty.[169] The mechanism of such difficulty involves hyaline changes in the lung but to be clinically significant as a cause of death requires the addition of 70 per cent pulmonary atelectasis.[169-171] The hyaline changes are statistically best correlated with prematurity, cesarean section, diabetes and multiple births in that order.[171] The first three are frequently combined in diabetic pregnancies. The pathogenesis of the hyaline has been ascribed to anoxia.[170]

Hoet[160] has gathered evidence for significant environmental in addition to hereditary causation of both the immediate fetal abnormalities and the future tendency of the offspring to become diabetic.[160] There is increased maternal corticosteroid production,[172] and this is accompanied by transfer of the steroids across the placental barrier.[173] Glucose is known to be so transferred.[174,175] The two together could co-operate to induce fetal hyperglycemia. This is compensated for by hypertrophy and hyperplasia of the pancreatic islets in fetuses of mothers with known and undiagnosed diabetes.[176*] Low blood sugars do indeed occur immediately after such infants are removed from the maternal environment[178,179]; in fact the low values found are inversely proportional to the maternal hyperglycemia.[178] The abnormal features of the diabetic fetus could conceivably be explained by these factors — the edema and water retention by the corticoids and the large size by the increased production of insulin, the growth function of which has been recently clarified.[3]

*This is associated with a peculiar eosinophilic infiltrate in a large percentage of cases.[177]

As for the second point, long term follow-up study of children of diabetic mothers has shown a larger incidence of diabetes (clinically, 9 per cent and by glucose tolerance test, 23 per cent) than might be indicated by heredity alone at that age.[159]

Attempts to reproduce this type of diabetic complication in lower animals have not been uniformly successful. In alloxan-diabetic rats, large offspring have been found predominantly among the males and, what is even more intriguing, in the second generation too.[180]

Study of renal function in women with glycosuria of pregnancy has shown that the glycosuria could be attributed to an imbalance between glomerular filtration and tubular reabsorption.[181] There are two types. In the first, the benign, the two functions are normal, with an absolute increase in glomerular filtration rate. The second is due to impairment of both functions, with the tubular damage relatively greater. In the latter, other evidence of renal disease is usually present and has been attributed to toxemia and hormonal abnormalities.

Complications

Metabolic Acidosis

In the treatment of diabetic acidosis the addition of fructose or glucose accelerates the reduction of ketonemia.[182] Fructose is no more effective in this regard than glucose, though more effective in reducing hyperglycemia. However, fructose has the disadvantage of increasing the urinary losses of potassium and sodium.[183] Since the diuresis of acidosis can be best correlated with solute load, and glucose ordinarily comprises almost half that load, glucose therapy would also increase the diuresis.[184] In experimental acidosis extracellular electrolyte concentrations are kept relatively constant, whereas the losses of water come mainly from muscle, those of sodium from bone, and those of potassium from muscle.[185] Since the heart retains its electrolytes tenaciously, it proves to be an insensitive index of total body losses of electrolytes.

The specific components of the electrocardiographic changes in pure hypopotassemia have been more clearly delineated,[186,187] and they tend to fall into four general patterns.[187] Certain coincidental conditions that may obscure these patterns should be sought for —namely, pre-existing heart disease; marked grades of hypertrophy of the left ventricle; bundle-branch block; anoxia; drugs; and other electrolyte influences. A base-line electrocardiogram is as important here as in all other cardiac conditions.

Close correlation between serum electrolyte levels and electrocardiographic changes is not always present. In normal subjects, chronic and moderate potassium depletion caused far fewer electrocardiographic changes than had been expected from the total losses.[188] Acute depletion produced by dialysis occurred

in two stages, a rapid drop in the first two hours, followed by a slower change over the next several hours.[189] Serum electrolyte homeostasis was again maintained at the expense of cells, but electrocardiographic changes were far greater than in the chronic experiment. The heart is apparently influenced more by the rate than by the magnitude of potassium losses.

In the therapy of acidosis, increase in insulin dosage[190] or the speed of its injection adds no advantage.

Degenerative Complications

General. The autopsy incidence of atherosclerotic complications in diabetes is ten times normal.[191] Clinical studies of large groups of patients with duration of diabetes of over fifteen years have appeared.[192-195] Only 20 per cent were free from vascular complications (large and small vessel) after twenty years.[192] There was a suggestive relation between increased incidence of atherosclerosis and poor diabetic control, and only 20 per cent of the general diabetic population studied was at all well controlled.[192,193]

The mechanism of the increased incidence of atherosclerosis in diabetes is still unknown. It is not clear whether the observed disturbance in lipid metabolism is of primary importance, only a synergistic factor, or merely secondary to renal disease.[196] Finally, interpretation of blood lipid values is difficult because the average control values used may not be derived from truly atherosclerosis-free individuals.

Some investigators have found no correlation in diabetes between atherosclerosis and elevation of either serum lipoprotein[197] or other lipid levels.[198] Paper-electrophoresis fractionation of serum proteins has shown a distinct rise in human diabetes of the major lipid-carrying beta-globulin fraction.[199] It has been reported by some that various lipid fractions rise out of proportion to the decontrol of the carbohydrate metabolic regulation.[200]

Qualitative variations of lipids have also been investigated. The colloidal stability of serum has been measured by turbidity changes after the in vitro addition of metallic salts (copper, zinc).[201] Atherosclerotic persons show decreased stability by this method. Increase of serum turbidity has been observed in vivo after insulin administration in both diabetic and nondiabetic persons.[202] Comparisons of lipid content of coronary vessels and blood in diabetic patients and the coronary arteries of diabetic and nondiabetic subjects have shown differences in the proportions of phospholipid components (mainly cephalin and lecithin) to each other.[203] This suggests that there may not be the complete identity of diabetic and nondiabetic atherosclerosis that has hitherto been assumed. A study of the rate of incorporation of P^{32} into blood phospholipid fractions (phosphoglyceride and sphingomyelin) revealed a distinct difference in the rates of incorporation of each of these two components in various disorders, including diabetes.[204]

In uncontrolled diabetes of rats the serum fatty acid (and, less so, the cholesterol and phospholipids) are elevated, as in the human counterparts.[205] Similarly, the diabetes of depancreatized dogs is accompanied by a rise in the "atherogenic" lipoproteins.[206] The paradoxical ameliorating effect of alloxan diabetes upon the development of cholesterol atherosclerosis in rabbits is due to the diabetes and not merely to the alloxan.[207]

Coronary atherosclerosis. The autopsy incidence of coronary occlusion is twice the normal rate in diabetes,[208] and the incidence of arteriosclerotic heart disease in a random adult diabetic clinic population is 40 per cent.[209,210] The poor immediate and long-term prognosis of diabetic patients with myocardial infarction has been statistically validated.[210] This report brought out the close interrelation of the attacks with acidosis, showing the need for proper treatment of the diabetes in patients with angina and for the use of insulin without hesitation.[211] Conversely, glycosuria and hyperglycemia in myocardial infarction should be regarded as indicative of diabetes until proved otherwise, and so treated (as in pregnancy).

The danger of hypoglycemia in precipitating myocardial infarction has been denied[210] and affirmed.[212] But, in a specific study employing insulin-induced hypoglycemia in 11 patients with known angina, no clinical angina was induced even though electrocardiographic changes occurred.[213] Such changes were regarded as not due to epinephrine release but to potassium changes. Moreover, hypoglycemia need not occur in an insulin-treated diabetic patient.

Peripheral vascular atherosclerosis. Peripheral vascular disease causes considerable morbidity among diabetic patients. This was demonstrated vividly by a recent survey of patients with this complication in eight large Massachusetts hospitals over a twelve-month period.[214] A total of 502 patients spent an average of twenty-six hospital days each, with a total hospital cost of $500,000, excluding nursing and medical costs. This did not include an equal prehospital and an incalculable posthospital period; nor did it include loss of income.

There are many preventable precipitating factors among such cases, as well as faulty therapy by patient or physician before hospitalization.[214,215] The higher incidence of gangrene in peripheral vascular disease of diabetics as compared with nondiabetic persons[216] is attributable to many factors, including increased susceptibility to infection and the more distal localization of the vascular obstruction in diabetes.[216]

The recent successful attempt to improve circulation by arterial grafting is a fundamental approach to the problem.[217] The peripheral location of the obstruction in diabetes makes this less applicable to diabetic patients. With the co-operation of Dr.

Sydney Brass, of the chiropody clinic of the Beth Israel Hospital, I have had gratifying success with the fitted "impression depth" shoe in healing and preventing recurrence of indolent foot ulcerations in the diabetic (and nondiabetic) foot attributable to ischemia or neuropathy or both.

Diabetic nephropathy. Experimental kidney lesions remarkably similar to those in the human patient have been produced in alloxan diabetes or cortisone treatment of rabbits.[218,219] The sequence is first capillary dilatation,[219] and then infiltration of an eosinophilic material interstitially, the nodular lesions being rarest of all.[218] There is a closer similarity in staining characteristics between human and experimental exudative lesions than between human exudative and nodular lesions.[218,220] Lipemia is involved in the pathogenesis of experimental lesions. This is so for lesions of choline-deficient rats[220] and in cortisone-treated rabbits.[219] In the latter heparin prevented both the hyperlipemia and the renal lesions.[221] Yet it is equally clear that many other conditions with simple lipemia do not have such lesions.

In the human disease, the problem is to evaluate the relative importance of the observed pathological findings. Further study suggests that a diffuse thickening of the glomerular basement membrane is a quantitatively important lesion,[222] even though the nodular lesions are shown to be very distinct from all the others qualitatively.[223] This confirms the finding of ultraviolet microscopy,[224] which also has exonerated the larger renal vessels from pathogenic significance.[225]

The use of aspiration renal biopsy[226] has thrown light on the developmental sequence of the lesions in human beings: the diffuse lesion is early, and the nodular late. And, as might be expected, there is much better correlation between clinical diabetic nephrosis and the diffuse lesions.[227] Capillary aneurysms are late, rare and distinctly subordinate lesions in human diabetic nephropathy, unlike the experimental disease (discussed above) or in the eye.[226]

Because the lesions in both diabetic nephropathy and retinopathy show a distinctive carbohydrate-staining material, estimates have been made of protein-bound carbohydrate of serum in diabetes. These are elevated, especially in patients with nephropathy.[228-231] One component of this group, glucosamine, shows a dynamic relation to blood sugar, each rising and falling within minutes of one another.[232] Serum lipid elevations in human diabetes also show a closer relation to renal complications than to any other factor (except perhaps control).[233] But their pathogenic significance is not yet decided.

The increased capillary fragility of diabetic patients has suggested that nephropathy and retinopathy may be but localized manifestations of a generalized small-vessed defect. Ditzell and Sagild[234] have described morphologic changes in the bulbar conjunctival capillaries and venules of diabetic patients. Although the magnification used was not large and the findings not absolutely specific for diabetes, the incidence was greater in persons who were known to have diabetes, young or old.[235] It is possible that some local conditions peculiar to the kidney or retinal vascular bed may combine with this defect to produce the morphologically characteristic lesions.

Clinically, it has been suggested that some diabetic patients show amelioration of the diabetes with the development of the nephropathy.[236] Runyan et al.[237] have shown that this is not capable of statistical proof; yet this does not rule out its possible occurrence in individual cases. Since the kidney plays a part in degrading insulin, a renal lesion may be the functional basis for the diabetic phenomenon.

The incidence of hypertension, eye and kidney complications is large, being 60 per cent of each in a group of patients with onset of diabetes under forty years of age followed for five to twenty-five years; only 7 per cent were free of such complications after ten years.[238] This group was on a free diet. Additional studies continue to re-emphasize the element of poor control in predisposing to the development of diabetic nephropathy.[192,193,227,238,239,240]

The eye in diabetes. Study of experimental diabetic cataract underscores the importance of hyperglycemia in its pathogenesis since it is prevented by the lowering of blood sugar, by whatever means.[241,242] Yet it is not simply the physical effect of hyperglycemia, synergism with which has been demonstrated by d-galactose, d-xylose and l-arabinose, which have in common with glucose the same configuration at the second and third carbon atoms.[243,244] This is similar to the factors involved in the insulin effect on transport of sugars across cell membranes.

In cell-free extracts of rabbit lens lactic acid formation from various glucose and fructose phosphate compounds was studied.[245-247] It was concluded that the aerobic utilization of glucose by lens follows the Embden–Meyerhof pathway, as in other tissues. The speed of opacification of calf lens was then measured in a perfusion medium, and various chemicals were added with inhibitory properties at known stages in the metabolism of glucose.[248] A block either at the glycolytic or at the beginning of the citric acid cycle accelerated opacification — the former more. This completes the analogy with diabetic defects in other tissues.

The factors of duration[249,250] and lack of proper diabetic control have been found paramount for development of diabetic retinopathy. Retinopathy, though closely related to nephropathy, seems to precede the proteinuria.[250] It has been suggested that the diabetic complications and metabolic alterations are independent variables. The occurrence of typical eye changes in human hemachromatosis[251]

and surgical diabetes,[252] as well as less typical ones in experimental [253] diabetes, points to a dependence of this complication on the metabolic fault.

Because of the serious prognosis of diabetic retinopathy, a new major surgical approach has recently been proposed. This is based on the reported dramatic amelioration of diabetic retinopathy after pituitary failure,[254] and the reduction in severity and lability of experimental diabetes after hypophysectomy or bilateral adrenalectomy.[255,256] Hypophysectomy has proved to be more frequently beneficial to the eye lesions than bilateral adrenalectomy.[257,258] Neither affected the course of the nephropathy significantly, and moderate to severe renal disease is considered a contraindication. The effect on hypertension complicates the interpretation of the therapeutic mechanism. This should be regarded as a purely experimental approach at present.

Neuropathy. The varied clinical manifestations of this complication have been emphasized by several clinical reports.[259-263] Lack of good control of known diabetes is more important in its development than duration.[259-262] Its occurrence in undiagnosed diabetes is an indication for the use of a glucose tolerance test in atypical syndromes, which can suggest myelitis as well as neuritis and can have predominantly motor signs, although associated with pain.[263] Autonomic-nervous-system involvement is frequently overlooked if only clinical manifestations are looked for.[259,260] Ocular palsies tend to be isolated findings, and are sometimes preceded by unilateral headache.[264] The prognosis varies; it is much better with eye or limb involvement than with autonomic neuropathy. There is only 50 per cent recovery from diarrhea and practically none from impotence or neuropathic foot lesions.[260] Recovery, when it occurs, takes three or more months and is gradual and remittent in its course. Of all therapy proposed, normoglycemia and bed rest are still the most effective.[261]

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MEDICAL INTELLIGENCE

FATAL POISONING WITH METHYPRYLON (NOLUDAR), A NONBARBITURATE SEDATIVE*

WILLIAM U. REIDT, M.D.†

ALBANY, NEW YORK

METHYPRYLON (Noludar), 3,3 diethyl-2,4-dioxo-5-methylpiperidine, is a nonalkaloidal, nonbarbiturate central-nervous-system depressant recently made available for general use. It is a derivative of 3,3-diethyl 2,4-dioxo-piperidine (Sedulon), a sedative cough syrup. A review of the recent literature has not revealed a previously reported case of fatal poisoning with this drug. It is for this reason that the following case is presented.

CASE REPORT

A 64-year-old retired male schoolteacher was admitted to the hospital on August 27, 1955, in a comatose state. He had last been seen awake at about 7 p.m. on the preceding day, when he retired to his room. At 11 a.m. on the day of admission, he was found by his wife to be asleep and unresponsive. An empty bottle of Noludar, which had contained an estimated 30 200-mg. tablets, was found at the bedside. The patient arrived at the hospital 18 hours after he was last known to be awake.

The past history revealed that he had made a suicide attempt with barbiturates in September, 1954. He had remained unconscious for 96 hours at that time. Psychiatric study revealed features of a typical reactive depression thought to be due to loss of interests on retirement and aggravated by failing vision. Recovery was satisfactory after 5 electro-shock treatments. He was discharged from the hospital in March, 1955, after undergoing cyclodialysis for treatment of glaucoma. A diagnosis of argyria due to prolonged use of argyrol for chronic rhinitis was also made.

On arrival, the patient was deeply comatose. There was grayish-blue discoloration of the eyelids, face, lips and nail beds. Corneal reflexes were absent, and the pupils did not react to light. The neck was flaccid. Chest excursions were markedly diminished, and breath sounds were barely audible over the upper-lung fields. Percussion was normal; no rales were heard. The heart was questionably enlarged, the maximal impulse being felt to the left; rhythm was irregular owing to premature contractions, and there were no murmurs. The abdomen was normal. Neurologic examination revealed no response to painful stimuli and absent superficial abdominal and deep tendon reflexes. No pathologic reflexes were elicited.

The temperature was 96°F., the pulse 72, and the respirations 20. The blood pressure was 80/56.

The hemoglobin was 16.5 gm. per 100 ml., the hematocrit 62 per cent, and the white-cell count 8350, with 84 per cent neutrophils, 15 per cent lymphocytes and 1 per cent basophils. Urinalysis was negative except for a trace of albumin and an occasional granular cast per high-power field in the sediment. The blood nonprotein nitrogen was 68 mg., the sugar 102 mg., and the calcium 8 mg. per 100 ml. The carbon dioxide combining power was 14 milliequiv., the sodium 138 milliequiv., the potassium 4.8 milliequiv., and the chloride 92 milliequiv. per liter. The spinal fluid contained no cells but showed 114 mg. per 100 ml. of sugar, 110 milliequiv. per liter of chloride and 36 mg. per 100 ml. of protein. The reaction for globulin was negative. An electrocardiogram was normal except for sinus tachycardia. X-ray study revealed clear lung fields.

On admission an infusion of 1000 ml. of 5 per cent glucose in saline solution was started, an endotracheal tube was inserted to maintain a patent airway and facilitate removal of secretions, and oxygen was given by nasal catheter. A polyethylene tube was anchored into the saphenous vein for prolonged intravenous infusion, and an indwelling catheter was inserted in the bladder. Penicillin was started, and tracheal suction was carried out at frequent intervals. Intravenous caffeine and sodium benzoate, 0.5 gm., given on 2 occasions was without effect. At this time 12 mg. of nor-epinephrine in 1000 ml. of 5 per cent glucose in water was started. Thereafter, continuous infusion of nor-epinephrine was required to maintain adequate blood pressure.

Twenty-four hours after admission the patient was still comatose, with absent reflexes and no response to painful stimuli. Despite a fluid intake of greater than 2000 ml., the output of urine totaled only a few milliliters during the first 24 hours. Thereafter, the output increased, reaching a maximum of 850 ml. on the 4th hospital day. Examination of the urine showed a fixed specific gravity, with many red cells and white cells and casts in the sediment, indicating that tubular damage had occurred. The blood nonprotein nitrogen rose from 68 mg. per 100 ml. on admission to 133 mg. on the 5th hospital day. The serum sodium fell from 138 milliequiv. to 120 milliequiv. per liter, and the serum chlorides from 102 milliequiv. to 84 milliequiv. per liter. The carbon dioxide combining power rose from 14 milliequiv. to 23 milliequiv. per liter. The serum potassium remained within normal limits until the day of death, when it rose to 7.3 milliequiv. per liter.

Because of the necessity of continuing nor-epinephrine to maintain blood pressure and at the same time of limiting fluids, the concentration of nor-epinephrine was increased to 24 mg. per liter of fluid. Despite these measures, subcutaneous edema appeared on the 3d hospital day, indicating overhydration.

By the 3d day the depth of ventilation had increased, and there was good air exchange. Bronchial breath sounds were heard at the right base, and x-ray examination confirmed the presence of pneumonia. The endotracheal tube was removed, and tracheostomy was done. Intratracheal suction yielded a large amount of thick, yellow mucus. Blood studies at this time showed an arterial oxygen saturation of 87.6 per cent, carbon dioxide content of 32.5 vol. per cent, carbon dioxide pressure of 28.3 mm. of mercury and pH of 7.40. Oxygen therapy, which had been discontinued when respirations improved, was reinstituted. Also at this time the left triceps reflex had reappeared, but no other reflexes could be elicited. Jaundice was noted on the 3d day, and liver-function studies revealed an elevated bili-

*From the Medical Service, Albany Veterans Administration Hospital. †Instructor in medicine, Albany Medical College.

rubin, 3.7 mg. per 100 ml. direct and 6.6 mg. total. The prothrombin time and thymol turbidity were normal.

Attempts to discontinue nor-epinephrine were made several times, but on each occasion the blood pressure dropped to shock levels. On the 4th day 100 mg. of hydrocortisone was given intravenously, and 50 mg. of cortisone intramuscularly, despite the absence of clinical and laboratory evidence of adrenal insufficiency. This did not prevent marked hypotension when nor-epinephrine was stopped. Mephenpermine (Wyamine) given intramuscularly was also unsuccessful in maintaining an adequate blood pressure.

On the 5th day respirations became labored, the skin was cold and clammy, and cyanosis increased. The patient died without regaining consciousness.

At autopsy the lungs showed a severe degree of pulmonary edema and moderately advanced bilateral lobular pneumonitis. Microscopical examination revealed areas of acute bronchopneumonia, with extension of the suppurative process into the adjacent parenchyma. Vascular congestion and diapedesis of acute inflammatory cells into collapsed alveolar areas were present. Grossly, the kidney appeared normal except for some blue-gray discoloration at the calyceal tips suggestive of argyria. Sections showed moderately severe, cloudy swelling and some dilatation of the tubules in the region of the loops of Henle. The liver weighed 1750 gm. and was congested and swollen, with a significant degree of fatty metamorphosis. On microscopical section there was, in addition, a mild degree of bile stasis in the bile canaliculi. There was no evidence of cirrhosis. Grossly, the brain was normal. Microscopically, there was moderate perivascular and parenchymal edema. Several small areas of dissolution of brain substance were seen.

Blood taken at autopsy was analyzed for Noludar according to the method recommended by the manufacturer. No evidence of its presence was obtained. A specimen of the liver was analyzed for volatile poisons, including alcohols, cyanides and chloroform, and for nonvolatile poisons, including barbiturates, alkaloids and analgesics. None were present in detectable amounts.

Discussion

According to literature supplied by the manufacturer,[1] clinical studies by Cass et al. on the hypnotic effects of Noludar on patients with insomnia established 200 mg. as the dose from which most patients could derive an adequate night's sleep. Loughlin et al.[2] compared the hypnotic effects with those of certain barbiturates. Their observations suggest that 250-mg. doses of Noludar and 100-mg. doses of secobarbital (Seconal) or pentobarbital (Nembutal) have similar hypnotic effects. Severe poisoning with barbiturates occurs when the amount of drug taken exceeds ten to fifteen times the usual hypnotic dose.[3] It is estimated that 30 Noludar tablets of 200 mg. each were taken by the patient. With the same criteria, it is apparent that ingestion of this amount of drug represents severe poisoning.

The findings exhibited by the patient were those of marked central-nervous-system depression similar to the changes accompanying severe acute poisoning with barbiturates. Most striking was the hypotension, which required continuous administration of a vasopressor drug to maintain the circulation. The functional and anatomic alterations of the liver and kidney are thought to have resulted from hypotension and not from any specific action of Noludar. It is probable that shock also contributed to the extensive pulmonary edema that was the immediate cause of death. It is of interest that pulmonary complications were not prevented by intensive penicillin therapy, tracheostomy and frequent changing of the patient's position. Respiratory depression, although present on admission, disappeared with time and required no mechanical aids in treatment.

The failure to identify Noludar in the blood was disappointing, but thought not to be inconsistent in view of the five-day interval between the ingestion of the drug and death. The absence of other detectable poisons in the liver, including barbiturates, is considered confirmatory evidence of the diagnosis of Noludar poisoning.

Summary

A fatal case of poisoning by Noludar is reported. This drug is capable of producing a profound central-nervous-system depression not unlike that seen with severe barbiturate poisoning. The autopsy findings are thought to be secondary to prolonged shock and not related to any specific effect of the drug.

Since this manuscript was submitted for publication, the manufacturers have informed me that they have reports on 14 patients who, in suicidal attempts, ingested overdoses of Noludar ranging from 2 to 9 gm.; 6 had taken 3 gm. or more. All recovered uneventfully. The case reported above therefore, to my knowledge, represents the only case of fatal poisoning so far reported.

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DOCTORS AFIELD

Richard Jordan Gatling, M.D.

Edward Shapiro, M.D.*

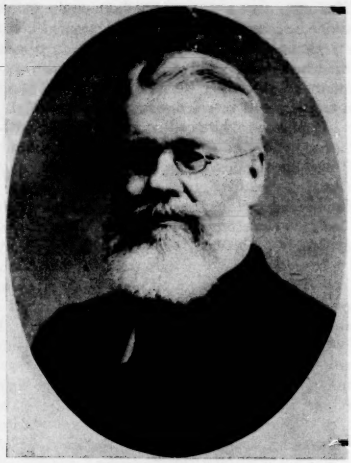
Los Angeles, California

AMONG historians there may be some dispute whether Richard Gatling, M.D., the inventor of the machine gun known by his name, was a doctor afield or an inventor afield. However, in Dr. Gatling's mind there was no question. Although he was thirty years old before he entered medical school and never actually practiced the healing art, he was ever afterward, by personal preference, known and addressed as "Doctor." In military textbooks and popular magazines, as far back as *Harper's Weekly* of 1898 and as recent as *Life* of 1955, references to his name are invariably prefixed by his medical title.

Richard Jordan Gatling was born in Hertford County, North Carolina, on September 12, 1818. His father was a well-to-do planter, the owner of numbers of acres and slaves. The boy was given the ad-

*Associate clinical professor of medicine, University of Southern California School of Medicine; chief, Cardiac Clinic, Cedars of Lebanon Hospital; senior attending physician, Los Angeles County Hospital.

vantage of all the education the neighborhood could offer. However, his father did not indulge him. Young Richard was encouraged to become a good penman, and for his pains he spent most of his sixteenth year copying records in the county clerk's office. When he was but nineteen, he taught school. In his spare hours, he worked jointly with his father



on an invention for sowing cotton seeds and a device for thinning out seedlings. Encouraged by the successful use of these machines, Richard decided upon inventing as a career. By the time he reached voting age, he had perfected a practical screw propeller for steamboats, only to learn that a patent for a similar device had been granted a few months earlier to John Ericsson (who was later to design the ironclad *Monitor*). Richard established himself in St. Louis, where he modified his cotton-sowing machine for the planting of rice, wheat and other grains. These implements did much to increase agricultural production in the Middle West.

In the course of selling these machines during the winter of 1845-46, he traveled by steamer from Cincinnati to Pittsburgh. On this voyage he was stricken with smallpox and lay unattended for thirteen miserable days while the ship was icebound in mid-river. This horrible experience induced him to study medicine simply to be able to take care of himself and his family during the frequent smallpox epidemics that regularly ravaged the country. He gave up his prospering business to attend medical lectures at the Indiana Medical College in 1847-48. He graduated at the age of thirty-two from the Ohio Medical College at Cincinnati in 1850. In the same year he invented a hemp-breaking machine. There is no record that Richard Gatling, M.D., ever practiced medicine. After his graduation he moved to Indianapolis to manufacture and sell his seed-sowing machines. In 1857, he invented a steam plough.

At the outbreak of the Civil War, Dr. Gatling reversed the customary process of beating ploughshares into swords. The idea of a rapid-fire gun had been in the minds of countless inventors. But it could not be made into a practical weapon until a satisfactory metallic cartridge had been evolved in 1860. In 1862 Gatling patented a machine gun that could fire 250 shots per minute. It consisted of 5 to 10 barrels of musket caliber that rotated about a shaft. The firing speed was controlled by a hand crank. Each barrel was loaded by gravity as it made a half-revolution around the central shaft. The barrel was then fired. During the second half-revolution the cartridge was extracted and ejected. The Civil War was nearly over before the federal authorities adopted the Gatling gun as official ordnance. However, other countries became interested. As one writer sanguinely phrased it, "the invention was adopted by almost every civilized nation." Dr. Gatling's gun remained standard ordnance until it was superseded in World War I by weapons in which the energy of discharge was used to eliminate the hand crank. By that time he had been dead more than a decade.

Today, his agricultural implements are obsolete. His machine gun finds a place only in museums. His name, however, remains diminutively enshrined in American slang as the word "gat," the gangster's term for his pistol.

123 North San Vicente Boulevard (Beverly Hills)

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CASE RECORDS
OF THE
MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 42311

PRESENTATION OF CASE

First admission. A sixty-four-year-old spinster was admitted to the hospital because of disorientation.

Historical details were sketchy because of the patient's mental status and the lack of observers. Apparently, she had had some type of heart disease for many years. One year previously she was committed to a mental hospital. There was a past history of episodes of sudden onset of dyspnea, orthopnea, sweating, weakness, apprehension and fibrillation. Six months before entry she had "dropsy." She had been taking digitalis irregularly, as well as mercurial diuretics and aminophylline, and was on a low-salt diet. Several weeks before admission gradually increasing tachypnea and a cardiac arrhythmia were noted. The arrhythmia was controlled with quinidine therapy. During the two weeks before entry she was nauseated, and there were occasional episodes of vomiting. One week before admission there was an episode of dyspnea, orthopnea, weakness, sweating, apprehension and fibrillation similar to those that she had had in the past. In spite of digitalis and quinidine therapy the dyspnea persisted. She was oriented as far as was known until two days before entry, when she became oliguric and increasingly lethargic, stuporous and disoriented.

Physical examination showed a thin, wasted, dehydrated, disoriented woman who was weak and dyspneic. The scleras were slightly icteric. The veins of the neck were distended to the angle of the jaw. Examination of the lungs revealed fine, sticky rales at both lung bases. The left border of cardiac dullness was at the anterior axillary line in the fifth intercostal space. There was atrial fibrillation. The pulmonic second sound was greater than the aortic. The mitral first sound was slightly accentuated. A Grade 2, apical, systolic murmur that radiated into the axilla and toward the left sternal border and a Grade 1 to 2 apical mid-diastolic rumble were audible. The liver edge, which was smooth, firm and slightly tender, was palpable 4 fingerbreadths below the right costal margin. The spleen was not felt. There was + pretibial edema. Both feet were cold, with violaceous skin. The dorsalis-pedis and posterior-tibial pulsations were absent bilaterally. The femoral and popliteal pulses were present.

The temperature was 100°F., the pulse 120 and irregular, and the respirations 40. The blood pressure was 110 systolic, 80 diastolic.

The urine gave a + test for albumin; the sediment contained occasional white cells, a rare red cell and many hyaline casts per high-power field; a culture showed no growth. The creatinine clearance was 26 liters and 41 liters per twenty-four hours. Examination of the blood revealed a hemoglobin of 12.1 gm. per 100 ml. and white-cell count of 36,400, with 82 per cent neutrophils. The nonprotein nitrogen was 177 mg., the calcium 9 mg., the phosphorus 2.5 mg., the total protein 7.5 gm., the albumin 5 gm., the globulin 2.5 gm., the creatinine 2.2 mg., the uric acid 6.2 mg., the cholesterol 161 mg., the bilirubin 1.1 mg. direct and 2.1 mg. total, and the fasting blood sugar 111 mg. per 100 ml. The sodium was 125 milliequiv., the potassium 6.1 milliequiv., the chloride 98 milliequiv., the carbon dioxide 14 milliequiv., and the total solutes 326 and 284 milliosmols per liter. The pH was 7.38. The alkaline phosphatase was 5.1 units. The prothrombin content was 14 per cent. The transaminase was 246 units. The blood showed no detectable bromide and 0.1 mg. per 100 ml. or less of barbiturates. The serum electrophoretic pattern was normal except for a slight increase in the gamma globulin. The blood Hinton test was negative. Numerous blood cultures showed no growth. X-ray films of the chest demonstrated a greatly enlarged heart; fluid was present in both pleural spaces; the hilar vessels were slightly accentuated, but the peripheral lung fields were not unusually congested; there was some hazy density in the right lower lung (Fig. 1). An abdominal film showed a density consistent with calcified lymph nodes in the left middle portion of the abdomen; the visualized bones were demineralized; there was some deformity of the upper margin of the second lumbar vertebra; the liver was questionably enlarged. Electrocardiograms showed persistent left-bundle-branch block, with atrial flutter and fibrillation.

The patient was digitalized and given sodium bicarbonate and saline solution intravenously. The urinary output increased to normal, and by the sixth hospital day the serum nonprotein nitrogen was 27 mg. per 100 ml. A phenolsulfonphthalein test was negative. The serum transaminase was 66 units on the tenth hospital day. The dyspnea subsided, the veins of the neck were no longer distended, and there was improvement in mental function. The discoloration of the left foot gradually subsided, and a good dorsalis-pedis pulse became palpable. The toes of the right foot remained cyanotic, and the dorsalis-pedis pulse continued to be absent on that side. There was never any tenderness or pain in the calves. Because of the gradual development of a pleural effusion on the right, a thoracentesis

was performed on the sixteenth hospital day, 850 ml. of serosanguineous fluid containing fibrin being obtained; the specific gravity was 1.018, and the cell count was 13,200, including 900 red cells and 12,300 white cells per cubic millimeter, with 80 per cent neutrophils and 20 per cent lymphocytes and mononuclear cells; the total protein was 3.5 gm. per 100 ml.; cytologic examination for malignant cells was doubtful; smears were negative for acid-fast bacilli; guinea pigs inoculated with the fluid gave no evidence of tuberculosis; a culture showed no growth. X-ray films of the chest three days later again disclosed an enlarged heart, with definite prominence of the left atrium; there were discrete areas of density in the right-lung field; an area of density adjacent to the hilar region presented a round, sharply demarcated margin; the lower third of the right-lung field was partially obscured by a density with a rounded, sharply demarcated upper margin; there was some

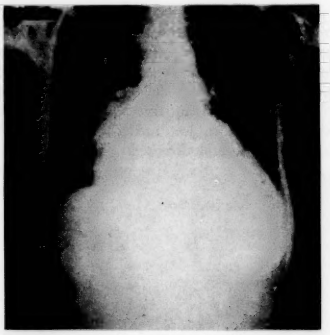

FIGURE 1. *Roentgenogram of the Chest Taken on Admission, Showing the Generalized Cardiac Enlargement and Moderate Engorgement of the Pulmonary Vessels.*

fluid in the right pleural space (Fig. 2). At this time the serum bilirubin was 0.7 mg. per 100 ml., and a bromsulfalein test showed 17 per cent retention. The temperature ranged between normal and 100.4°F., and the white-cell count between 13,200 and 18,500. The prothrombin content was 50 per cent. The patient continued to show progressive improvement and was discharged afebrile on the twenty-third hospital day.

Second admission (seven weeks later). In the interval she did well until four days before entry, when there was an acute episode of dyspnea. The next day the dyspnea recurred and was associated with much coughing but no pain or hemoptysis. With oxygen therapy and two injections there was much improvement. On the day of admission she was brought to the emergency ward in acute pulmonary edema that was relieved with tourniquets, oxygen and morphine.

Physical examination on the ward showed her to be oriented and in no acute distress. The veins of the neck were not distended. Examination of the chest revealed dullness over both lung bases, with diminished breath sounds and tactile fremitus as well as crackling moist rales. The left border of cardiac dullness was percussed 1 cm. to the left of the mid-

FIGURE 2. *Roentgenogram of the Chest Taken on the Nineteenth Hospital Day.*

The heart appears larger and more triangular than previously. There are now two dense areas in the right lung — the larger at the base, and the smaller opposite the hilus.

clavicular line. The rhythm was irregular. Murmurs were as previously described. The pulmonic second sound was equal to the aortic. There was no periph-

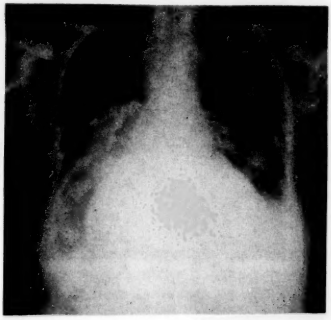

FIGURE 3. *Roentgenogram of the Chest Taken on the Second Admission.*

The congestive changes in the lung, with pulmonary edema, are marked, and there are small bilateral diffusions.

eral edema. Examination of the abdomen was negative. The right foot was cold and pulseless; the toes looked better than previously.

The temperature was 100.8°F., the pulse 150 and irregular, and the respirations 20. The blood pressure was 110 systolic, 60 diastolic, with 12 mm. of pulsus paradoxus.

The urine gave a + + + test for albumin, a green test for sugar and a + + test for acetone; the sedi-

ment contained numerous white cells and a few granular casts per high-power field; a culture grew out

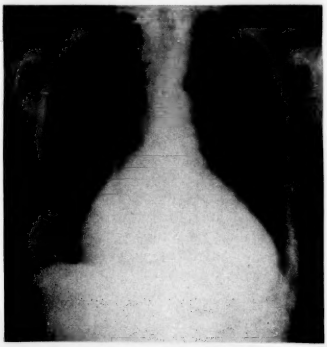

FIGURE 4. *Roentgenogram of the Chest, Showing That the Pulmonic Congestion is Considerably Less although Some Fluid Persists at Each Base.*

abundant coliform bacilli. Examination of the blood revealed a hemoglobin of 12.8 gm. per 100 ml. and a white-cell count of 21,200, with 85 per cent neutrophils. The serum nonprotein nitrogen was 38 mg., and the fasting blood sugar 91 mg. per 100 ml. The serum sodium, potassium, chloride and carbon dioxide were normal. The prothrombin content was 60 per cent. The serum transaminase was 60 units. X-ray films of the chest demonstrated a diffuse granular density occupying both lung fields, with a pleural effusion on the left (Fig. 3); the previously noted discrete areas of consolidation in the right side of the chest were no longer present; the heart showed no appreciable change in size. An electrocardiogram revealed left-bundle-branch block and atrial-flutter fibrillation at a rate of 140; the axis was normal; subsequent tracings showed slowing of the ventricular rate. A thoracentesis on the left side yielded 60 ml. of grossly bloody fluid; cytologic examination for malignant cells was unsatisfactory.

On the second hospital day a bilateral superficial-femoral-vein ligation was performed; no thrombi were found. On the fifth postoperative day x-ray films of the chest showed a decrease in the pleural effusion on the left; the lung fields were clear except for some congestion and an area of density in the right-lower-lung field; there was no appreciable change in the size of the heart. X-ray films of the chest five days later showed complete clearing of the fluid in the left pleural space and residual pleural thickening in the right costophrenic angle (Fig. 4); the heart was slightly smaller; no intracardiac calcification was seen at fluoroscopy. The patient was discharged improved on the eleventh postoperative day.

Final admission (four weeks later). Conflicting data were obtained about the interval history. She apparently had been taking digitalis irregularly. She stated that she had had abdominal pain on movement in the right upper quadrant for a week or two before entry. During this time there was paroxysmal nocturnal dyspnea, orthopnea and a mild, unproductive cough. There was no edema of the ankles. As she was being examined in the Emergency Ward the blood pressure and pulse gradually became unobtainable, and she responded only to painful stimuli.

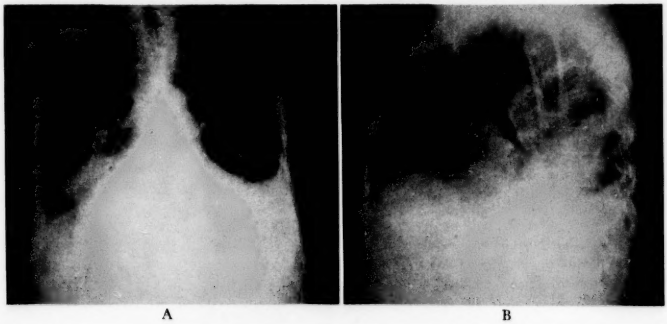

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FIGURE 5. *Roentgenograms of the Chest Taken on the Final Admission, Showing Recurrent Areas of Density on the Right Similar to Those Observed at the Time of the First Admission. There is also a large pleural effusion on the left.*

Physical examination on the ward showed her to be somewhat more responsive although the blood pressure was still unobtainable. The veins of the neck were distended to the angle of the jaw when she was elevated 60°. Examination of the chest revealed dullness over the left-lung base and moist rales over both lung bases. The heart was as previously noted. The liver edge, which was slightly tender, was felt 4 finger-breadths below the right costal margin. There was + to + + pitting edema of the legs up to the knees.

The temperature was 99.2°F., the pulse 160 and irregular, and the respirations 40.

The urine gave a + + + test for albumin; the sediment contained 10 to 20 white cells and many bacteria per high-power field; a culture grew out a moderate number of coliform bacilli. Examination of the blood revealed a hemoglobin of 12 gm. per 100 ml. and a white-cell count of 16,000, with 81 per cent neutrophils. The nonprotein nitrogen was 100 mg., the total protein 6.6 gm., the albumin 4.2 gm., the globulin 2.4 gm., the bilirubin 0.9 mg. direct and 1.1 mg. total, the salicylates 2.5 mg., the creatinine 3.3 mg., and the fasting blood sugar 106 mg. per 100 ml. The serum sodium was 128 milliequiv., the potassium 6.6 milliequiv., the chloride 100 milliequiv., the carbon dioxide 10 milliequiv., and the total solutes 312 milliosmols per liter. The transaminase was 60 units. A throat culture grew out moderate numbers of *Haemophilus influenzae* and a few *Staphylococcus aureus*, beta-hemolytic streptococci, *Neisseria catarrhalis* and nonhemolytic streptococci. X-ray films demonstrated a large pleural effusion on the left and a marked increase of the fluid on the right (Fig. 5); increased pulmonary vascular congestion was noted; the heart size was difficult to evaluate because of the fluid. An electrocardiogram showed left-bundle-branch block and atrial fibrillation. A thoracentesis on the left side yielded 400 ml. of serosanguineous fluid with a specific gravity of 1.006.

Despite oxygen, Cedilanid, aminophylline, tourniquets and intravenous administration of Levophed, intractable pulmonary edema occurred, and the blood pressure remained unobtainable. She died four days after admission.

Differential Diagnosis

Dr. Felix G. Fleischner*: At the time of the first admission, this sixty-four-year-old woman had had long-standing heart disease with episodes of fibrillation and decompensation as well as episodes that appeared to result from pulmonary embolism. She did not have calf tenderness or other evidence of peripheral thrombophlebitis, and at the time of the second admission, when the leg veins were tied, no thrombi were found. A third of pulmonary emboli come from the veins of the lower extremities, a third from the pelvic veins, and a third from the heart. In cases of mitral stenosis with pulmonary emboli, 25 to 35 per cent of the emboli originate from thrombi in the right atrium or right ventricle. Therefore, the absence of thromboses in the legs does not rule out pulmonary emboli. The violaceous skin of the feet may have been caused by vasospasm, advanced arteriosclerosis or hypoxemia as the result of the congestive heart failure. Of course, there may have been a localized thrombosis or an embolus from the left ventricle or a paradoxical embolus from the right side of the heart.

On the basis of the data from the first admission — the elevated nonprotein nitrogen, creatinine and potassium and the low creatinine clearance and chloride — I shall say that the patient had a uremic condition in addition to the congestive heart failure. I am not sure that the prothrombin content of 50 per cent is entirely explained by the congestive heart failure, but I shall not discuss this.

The first set of roentgenograms (Fig. 1), taken on the day after admission, reveal a large spherical heart. The hilar shadows are markedly increased, and the peripheral lung fields are bright and translucent. In roentgenograms taken on the nineteenth hospital day, the heart is triangular, and the aorta is not dilated (Fig. 2). The shape of the heart is not pathognomonic of any particular disease. I should like to see more prominence in the region of the third curve on the left, formed by the left atrial appendage. In the lateral view, the area of contact between the heart and the anterior wall of the chest is enlarged, but not as large as I should like to see it. The right-sided dilatation suggests relative tricuspid insufficiency, which goes with the enlarged liver. There are two areas of consolidation after most of the fluid has been removed. There is a possibility that these represent encapsulated fluid in the posterior portion of the interlobar fissure, but it is not evident in the films taken seventeen days previously and on the lateral view, so that I shall have to explain those shadows on the basis of pulmonary infarction. The vena cava is moderately dilated.

At the time of the second admission the roentgenologic findings and the history leave no doubt that the patient had acute pulmonary edema (Fig. 3). In the roentgenograms the central portions of the lung fields and to a lesser degree the peripheral portions are involved by confluent densities. There was a small pleural effusion on each side. The shadows attributed to infarcts apparently have faded. Most pulmonary infarcts are not of the permanent type, with necrosis and cicatrization, but are of the incomplete type, and eventually disappear in the roentgenogram. The picture is consistent with the residues of acute pulmonary edema, bilateral pleural effusion and probably tricuspid insufficiency.

There was nothing to call attention to the possibility of cardiac tamponade. The neck veins were not dilated; the vena cava was not seen on the roentgenograms, and the heart sounds were not said to have become distant. There was never a friction rub. The electrocardiogram does not help, for it revealed atrial fibrillation and left-bundle-branch block, which had been present from the beginning.

Thoracentesis yielded bloody fluid. Whenever we find bloody fluid, we think of three possibilities: tuberculosis, mostly in younger persons; pulmonary embolism, with infarction or even without infarction; and tumor. Grossly bloody fluid may accompany pulmonary edema, particularly if there is pulmonary infarction. The specific gravity and the cell count were entirely in keeping with pulmonary edema and embolism.

The patient rapidly recovered under the treatment

*Director, Department of Radiology, Beth Israel Hospital.

for acute pulmonary edema. The roentgenograms demonstrate clear lung fields (Fig. 4), but the heart is larger, with less pleural effusion on either side. Again, one may raise the question of pericardial effusion. The radiologist, as well as the clinician, has difficulty in distinguishing cardiac enlargement from a heart surrounded by a pericardial effusion. There is a small residual pulmonary infarct, and displacement is diagnostic of mitral stenosis.

At the time of the final admission, while the patient was being examined, the pulse and blood pressure became unobtainable. Did she have a ball-valve thrombus or a pedunculated tumor of the left atrium that suddenly obstructed the mitral ostium? I think these are farfetched possibilities. There is no mention that the change in blood pressure occurred with a change of position, and for the last four days the pulse remained unobtainable. Cardiac tamponade is a possibility, but there was no physical or roentgenologic evidence to substantiate that diagnosis.

During the second hospital admission there was evidence of urinary infection, more apparent during the final admission. There was no clue for old renal disease; therefore, I should call it pyelonephritis.

I have not yet mentioned the possibility of subacute bacterial endocarditis. A throat culture grew out moderate numbers of *H. influenzae*, *Staph. aureus*, beta-hemolytic streptococcus and *N. catarrhalis*, but apparently no blood cultures were done. There were no changes in murmurs, no peripheral vascular signs and no skin signs — nothing to substantiate the diagnosis of subacute bacterial endocarditis.

The final roentgenologic examination, made after the pulmonary edema had cleared again, reveals consolidation in almost the same place as it was seen during the first admission (Fig. 5). Again, there is pleural effusion, the cardiac silhouette is wider, and the superior vena cava is widened. We see dilatation of the azygos vein, which is the roentgenologic correlate of engorged veins in the neck.

It is not difficult to be sure of the events that were observed, but it is difficult to determine the underlying cause of them. I think that during the first hospital admission the patient was in congestive heart failure and uremia. In addition there was probably pulmonary embolism, with infarction on the right side; hemorrhagic pleural effusion; and peripheral arterial thrombosis or embolism. Were these events the result of myocardial infarction? Whether or not I can make this diagnosis depends on how definitely the transaminase determination provides evidence of myocardial infarction. In the past few years we have learned a great deal about serum transaminase. The normal values are between 10 and 40 units, but they may be as high as 60 or 70 units. In a recent article,* the serum transaminase was reported as being helpful in differentiating pulmonary and myocardial infarction. Values as high as 246 units, which is six or seven times the normal value, are considered to indicate myocardial infarction. The fact that the transaminase in the patient under discussion dropped from 246 units to 60 units seven weeks later tends to corroborate that diagnosis.

I might say a word about the infarct in the lung occurring in the same site during the third admission in which it appeared during the first admission. I should not be surprised if the pathologist found an organizing thrombus or embolus with recanalization in one of the larger pulmonary vessels on the right. Under such conditions another episode with thrombus formation may have caused the new infarct to occur in the same place.

I believe that the patient had old rheumatic valvular disease, with mitral stenosis and probably mitral insufficiency, and relative tricuspid insufficiency. Whether or not she had a myocardial infarct I cannot say. I shall leave that diagnosis to those who know more about the interpretation of transaminase values than I do. I do not think she died with cardiac tamponade. The blood pressure would be in keeping with this diagnosis, but there was no other evidence of it. Another possible immediate cause of death is an adrenal crisis, with low-sodium and high-potassium values, but I think this is a farfetched possibility. In addition, she probably had repeated pulmonary emboli, with infarction on the right, hemorrhagic pleural effusion and probably several episodes of pulmonary edema and urinary infection.

DR. BENJAMIN CASTLEMAN: Dr. Ropes, have you a comment?

DR. MARIAN W. ROPES: I saw the patient during the second admission. We agreed that pulmonary infarction was the best explanation of the x-ray findings. It was impossible to determine whether myocardial infarction had occurred at the time of the first admission. In spite of the fact that there was no evidence of thrombosis of the veins of the legs, we thought a ligation was worth performing. Obviously, that did not prevent further difficulty.

DR. FLEISCHNER: I think thrombi were found in the right atrium or ventricle and questionably on the left side of the heart.

CLINICAL DIAGNOSES

Rheumatic heart disease, with mitral stenosis and regurgitation and ? aortic stenosis.
Recurrent pulmonary embolism.

DR. FELIX G. FLEISCHNER'S DIAGNOSES

Rheumatic heart disease, with mitral stenosis and insufficiency and tricuspid insufficiency.
Pulmonary embolism with infarcts.
Pyelonephritis.

ANATOMICAL DIAGNOSES

Rheumatic heart disease, with mitral and aortic stenosis.

*Goldstein, F., Israel, H. L., and Seligson, D. Use of serum transaminase levels in differentiation of pulmonary embolism and myocardial infarction. *New Eng. J. Med.* **256**:746-749, 1956.

Hydrothorax, bilateral.
Interlobar fluid, right side of thorax.
Central congestion and necrosis of liver, severe.
Pulmonary atelectasis, bilateral.
Ascites.
Myocardial infarct, healed.
Mural thrombus, left atrium.

Pathological Discussion

Dr. Castleman: The findings at autopsy were a surprise to all of us. The heart was enlarged and showed rheumatic involvement of the mitral and aortic valves, both being stenotic. The right ventricle was not as thick as we expected it would be with that degree of stenosis. There was no fluid in the pericardium, but there was about half a liter of fluid in each thoracic cavity. On the right side, not only was there free fluid but also, as Dr. Fleischner hinted early in his discussion, some of the fluid was loculated. In the tissue between the upper and middle lobes there was a large loculated sac of fluid. The pleura was thick and ragged as a result of the previous collections of fluid on the right side. The lungs were small, weighing only 600 gm., and were collapsed by the fluid. We looked for recent and healed infarcts as well as emboli within the pulmonary vessels, but could find no evidence of them. In retrospect I suppose that the rapidity with which the shadows in the x-ray films disappeared is a clue favoring fluid rather than infarct. There was a small thrombus in the left atrial appendage.

As Dr. Fleischner had written a great deal about interlobar fluid, I thought that he was the only man in Boston who might consider it. He did, but discarded it.

Dr. Fleischner: You are kind in mentioning that. I thought of it but discarded it. As a matter of fact the diagnosis of infarcts or interlobar effusion cannot be made in many cases from the posteroanterior and lateral views of the chest. One has to determine by fluoroscopy the topographic relation to the pleura of the shadow-producing substratum.

Dr. Jacob Lerman: Were there coronary thromboses?

Dr. Castleman: There was an old myocardial infarct that may have been acute during the first admission when the transaminase was elevated.

Dr. C. Hollingsworth Smith: The patient had marked hepatic congestion and a liver described as 4 fingerbreadths below the right costal margin. That may account for the high transaminase.

Dr. Castleman: The liver was as severely congested as any that I have ever seen. Two thirds to three fourths of the liver was severely involved with congestion and necrosis.

Dr. Warren Point: Under such circumstances would not one expect more jaundice?

Dr. Castleman: There was no jaundice.

CASE 42312

Presentation of Case

A forty-four-year-old man entered the hospital because of abdominal pain.

Twenty-two years previously he noted abdominal pain in the right upper quadrant, which was relieved with an ulcer regimen. X-ray films allegedly demonstrated a duodenal ulcer. Subsequently, there were recurrent episodes of abdominal pain that were relieved with milk and antacids. Five years before admission there was marked exacerbation of the pain, which was crampy, was unrelated to meals and occasionally lasted several days. An upper gastrointestinal series was said to have shown a duodenal polyp. A Graham test was negative. During the year before entry the pain changed from a crampy character to a constant gnawing sensation that was relieved by food or antacids. There were also episodes of crampy pain in the lower abdomen, more marked on the right than the left, that was relieved with a bowel movement. A barium-enema examination three months before admission was negative. An upper gastrointestinal series two months later demonstrated a smooth, rounded, filling defect in the duodenal bulb measuring about 2 cm. in diameter and containing a small accumulation of barium within it near its center (Fig. 1); during the period of examination this lesion remained in the duodenal bulb and did not prolapse.

The patient had rheumatic fever twenty-nine years previously. Subsequently, there was slight aortic regurgitation and cardiomegaly, without functional impairment. There was a past history of bronchial asthma with infrequent wheezing recently. He had had known hypertension for three years, with a blood pressure of about 150 to 170 systolic, 100 to 120 diastolic.

Physical examination showed a well nourished man in no distress. There was no edema. The heart was enlarged to the left. The cardiac rhythm was regular, and the sounds were of good quality. The aortic second sound was greater than the pulmonic. A Grade 1 to 2, aortic, diastolic murmur was audible. Abdominal examination was negative.

The temperature was 98.4°F., the pulse 78, and the respirations 20. The blood pressure was 160 systolic, 100 diastolic.

The urine was normal. Examination of the blood revealed a hemoglobin of 14.8 gm. per 100 ml. and a white-cell count of 8700. The nonprotein nitrogen was 28 mg. per 100 ml. A stool specimen gave a negative guaiac test. X-ray films of the chest showed left ventricular enlargement and prominence of the aortic knob; the lung fields were clear. An upper gastrointestinal series demonstrated no changes from the previous examination.

An operation was performed on the fourth hospital day.

Differential Diagnosis

Dr. Frederick S. Tomchik*: I should draw from these films three conclusions. The first is that this was a tractable patient who took his medications faithfully, for in examinations on three different days radiopaque pills were seen within the abdomen. The second is that the pills were doing him no good, because they all arrived in the colon in a remarkable state of preservation. The third is that there was an abnormal mass in the duodenal bulb. Beyond that point we go from the science of deduction to the art of speculation. The clinical history indicated little more than that the patient probably had a benign process, and the x-ray films showed a small filling defect in the duodenal bulb that looked benign.

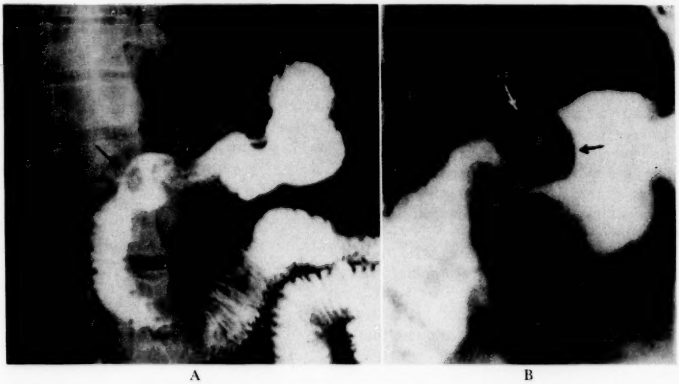
To review the films, the barium-enema examination shows nothing remarkable. The first gastrointestinal series demonstrates a normal stomach and a well filled duodenal bulb, with a round filling defect well visualized. The duodenal bulb itself shows no deformity. On the second examination the same filling defect, a small, round, radiolucent area that is sharply defined, is present. In the first set of spot films the duodenal bulb is not well filled, and I do not believe the lesion is outlined. A small, round, white spot overlying the region of the filling defect is seen on several of the spot films of the first examination. On the spot films of the second examination, however, which demonstrate the lesion much more clearly, the small white spot is not in evidence, but the barium produces a stellate shadow overlying the radiolucent defect. This stellate appearance is seen on three or four films.

*Clinical assistant in radiology, Massachusetts General Hospital.

The patient was originally given a diagnosis of duodenal ulcer. Whether he had a duodenal ulcer or not at that time I do not know. Many of these tumors and tumorlike masses in the duodenum reported in the literature, especially in the earlier years, were called ulcers radiologically. An acute duodenal ulcer can heal completely without causing deformity. However, if the patient originally had a bona fide duodenal ulcer and then continued to have symptoms for twenty-two years, it is almost certain that he would have had a considerably deformed duodenal bulb by the time of admission, so that I am inclined to doubt if he ever had a duodenal ulcer.

When confronted by a problem such as this, the radiologist tries to obtain both face-on and profile views of the lesion. This lesion is seen well on many of the films, but all are taken in the right anterior oblique or left posterior oblique position with the lesion face-on; it would be desirable to have films also at 90° from these positions — in other words, with the duodenal bulb in profile. In an obese patient such as this one, who has a high, transversely lying stomach, that view is difficult or impossible to obtain because when the patient is turned to the left anterior or right posterior oblique position, the antrum overlies the duodenal bulb. Also, we should like to apply graduated pressure to the bulb, to determine the ease with which the mass can be compressed, distorted or moved about and thus to learn more about the type of attachment to the wall of the bulb and about its consistence — whether it is firm or soft. Direct compression of the duodenal bulb is often impossible in a patient of this habitus.

I think it is obvious from the clinical history and from the appearance on the films that the lesion was



A B

Figure 1. *Films from the Gastrointestinal Series.*
A = *roentgenogram, showing the filling defect (arrow) in the proximal duodenum, with a stellate collection of barium at its center.*
B = *detailed view of the duodenal bulb, showing the filling defect (arrows).*

not malignant; therefore I shall not discuss the malignant lesions involving the duodenum. Of the tumors and tumorlike masses that affect the duodenum, the incidence is about equally divided between malignant and benign lesions; this is also true of the remainder of the small intestine. This is in sharp contrast to the situation in the stomach, where the ratio of benign to malignant lesions is about 1:160.

I have listed (Table 1) the common tumors and tumorlike masses of the duodenum, most of which have occurred in the duodenal bulb. This table is adapted from a summary of 68 cases that were collected by Hoffman and Grayzel.[1] Since the total was only 68 cases, the actual number of cases of each pathological type is low. Most of the tumors that have been described in the literature were probably asymptomatic and were found at autopsy or incidentally at abdominal exploration. However, these tumors more recently are being discovered and diagnosed radiologically with increasing frequency.

TABLE 1. *Tumors and Tumorlike Masses of the Duodenum.*

TYPE OF TUMOR	PERCENTAGE
Adenoma	32
Adenoma of Brunner's glands	11
Myoma	17
Aberrant pancreas	12
Hemangioma	8
Lipoma	7
Fibroma, lymphangioma, cystic masses, carcinoid, gastric rests	3 or less each

Physicians who have written about these duodenal tumors generally conclude that there is no clinical syndrome by which they can be recognized. The symptoms are usually those of upper gastrointestinal disease but are not specific. They may mimic the ulcer syndrome; the pain or epigastric distress may or may not be relieved by food or an ulcer regimen. There may be right-upper-quadrant rather than epigastric pain. Occasionally, the pain may be crampy, and the symptoms may be aggravated after eating, possibly as a result of a mechanical irritation caused when food passes through the duodenum.

The commonest tumor of the duodenum is the adenomatous polyp. The ordinary mucosal adenomas and the Brunner-gland adenomas together make up about 43 per cent of all these duodenal masses. The adenomatous polyp may be discovered at any age from infancy to old age. It may be sessile or pedunculated, and its surface may be lobulated, smooth or wrinkled. Usually, it is single, but it may be multiple, and it may be associated with gastric polyps. When one sees a polyp in the duodenal bulb or even farther down in the duodenum, one should always be aware of the possibility of a prolapsed gastric polyp. The proclivity to malignant degeneration of these polyps has not been as well established as it has been for gastric polyps. I encountered only 1 case report of an adenocarcinoma that was said to have arisen in an adenomatous polyp of the duodenum.[2] Radiologically, these polyps have no distinguishing characteristics except that they appear to protrude into the lumen and to arise from either the mucosa or the submucosa.

Brunner's glands are submucosal glands in the duodenum that secrete an alkaline, egg-white-like fluid. They form a continuous layer in the duodenal bulb and down toward the ampulla of Vater, but beyond the ampulla they become sparse and smaller and finally disappear completely at about the duodenojejunal junction. They are exceptionally well behaved glands; Robertson[3] indicates that they have a limited range of pathologic expression. However, solitary adenomas may arise from them; these present as a polypoid mass without any distinguishing radiologic features and would probably resemble the mucosal adenomas. Occasionally, the glands undergo hypertrophy, which may be diffuse or scattered. Spotty hypertrophy of the glands, when present, gives a radiologic pattern that we often describe as "cobblestone" in the first portion and proximal second portion of the duodenum. Cystic dilatation of these glands has also been described and gives an identical appearance. Multiple polyps of the mucosa also occur and produce a similar radiologic appearance. The lesion we are considering, of course, does not resemble that pattern at all.

The mesenchymal tumors — leiomyoma, neurofibroma, fibroma and so forth — form the great bulk of what the radiologists like to call intramural extramucosal tumors; that is, they arise within the wall of the viscus in the layers deep to the mucosa. The appearance may be quite characteristic[4]; they are usually sharply defined in the face-on view; they affect only a part of the circumference of the wall; they do not form a napkin-ring constriction as the carcinomas are apt to do; in profile view they typically present as an abrupt, hemispherical projection into the lumen, but without the overhanging margin forming an acute angle with the adjacent wall such as we usually see with a polyp. A lesion arising in the submucosa may produce either this appearance or the appearance of the typical mucosal polyp. Since the growth producing this bulge is beneath the mucosa, it tends to stretch the mucosa out over it, giving the bulge a smooth contour. About half these intramural extramucosal tumors ulcerate. The incidence of ulceration is somewhat higher with malignant than with benign types. Often, the ulceration takes the form of a small punched-out crater at the apex of the tumor and gives a characteristic radiologic appearance. When the malignant kind ulcerate extensively, it may be difficult to distinguish them from carcinoma. These lesions are commoner in the stomach than in the duodenum.

When we look at the first spot films, we see a fairly good imitation of an intramural extramucosal tumor. The white spot superimposed on the filling defect in the bulb is a good representation of a small ulcer in

the apex. On the large films, however, we see a similar-appearing round fleck of barium slightly away from the duodenal bulb. Therefore, I believe this spot of barium just happened to be superimposed on the lesion in the spot films. I think it represents a small amount of barium left behind in the colon from the previous barium enema and shall consider it an artifact.

Unfortunately, all the cases of so-called spindle-cell tumors do not present the classic appearance of an intramural extramucosal lesion. They may arise in the submucosa and protrude far into the lumen to simulate the appearance of a mucosal polyp.

Lipomas originate in the submucosa, but they almost routinely become pedunculated and mimic a mucosal polyp. Theoretically, one might be able to make a diagnosis of lipoma, if the lesion was of reasonable size, by detecting that it was somewhat more radiolucent than surrounding tissue with the radiodensity of water, but I do not know that decreased radiodensity has been demonstrated in vivo in a lesion as small as one of these polyps.

The cystic tumors of the duodenum are almost entirely enteric cysts or duplications. They are almost invariably discovered in the first two decades of life. Since these commonly arise deep within the wall of the viscus or are firmly attached to its exterior, they have the typical appearance of an intramural extramucosal tumor. I do not think that they would be likely to cause a picture like this. Occasionally, they may have calcification in their wall and might be diagnosed on that basis. I shall rule them out on the basis of the patient's age and the rather small size of the lesion.

Carcinoid arises in the submucosa of the duodenum, as well as elsewhere in the gastrointestinal tract, and could conceivably give the appearance either of a mucosal polyp or of an intramural extramucosal tumor. In the literature only about 15 in the duodenum are described. None, as far as I know, have been called malignant, but since the total number is low, we cannot be dogmatic about their lack of malignant potentiality in the duodenum.

Finally, I should like to discuss aberrant pancreas, which I think is the most interesting of these lesions. Aberrant pancreas is quite a common occurrence if one searches very carefully for small nodules. Feldman and Weinberg[5] searched a great number of duodenums routinely at autopsy and found a 14 per cent incidence of aberrant pancreatic nodules. The vast majority were under 1 cm. in diameter, and most were less than 0.5 cm. in diameter, so that they would usually not be detectable radiologically. Aberrant pancreas occurs in the stomach in about 25 per cent of cases, in the duodenum in about 30 per cent, in the jejunum in about 20 per cent and in other locations less commonly. Seven per cent of them are found in Meckel's diverticula. Other sites in which they have been found are in the gall bladder, bile ducts, omentum, mesentery and even the spleen. I believe that the nodules that are discovered radiologically are more commonly in the stomach than in the duodenum.

In many cases aberrant pancreatic tissue apparently causes no symptoms at all; in others it is difficult to decide whether the symptoms are due to aberrant pancreas or not. Barbosa et al.,[6] in 1936, reviewed 82 cases from the Mayo Clinic that had been encountered at operations and expressed the opinion that 60 per cent of these were the chief or a contributing cause of symptoms. Branch and Gross[7] described 24 cases, in 4 of which the ectopic pancreas was the site of a pathologic process. In 2 there were duodenal ulcers with hemorrhage, in 1 there was a pyloric ulcer (the ulceration in these cases having occurred in the tissues overlying aberrant pancreatic tissue), and in 1 there was a nodule in the pylorus that caused obstruction. In the small intestine nodules in several cases have caused intussusception.

The aberrant pancreatic tissue can be involved by any process that involves the normal pancreas: acute pancreatitis, carcinoma, islet-cell adenoma and so forth. The great majority of the aberrant nodules, however, are uninvolved by any pathologic process and either do not cause symptoms or cause them merely because of the presence of the mass.

About half the aberrant pancreatic nodules in the gastrointestinal tract are in the submucosa; the other half are within the muscularis and beneath the serosa. They rarely become pedunculated and usually present as an intramural extramucosal tumor or a sessile polyp. The overlying mucosa is usually intact; ulceration is unusual. They may show a small depression near the apex, which radiologically may closely mimic the punched-out ulcer of the spindle-cell tumors. However, almost always this is merely a localized depression or retracted area, not an ulceration. Therefore, if I saw a lesion showing the characteristics of an intramural extramucosal tumor and having a persistent fleck of barium near its apex, and repeated tests revealed no blood in the stools, I should lean toward a diagnosis of aberrant pancreas. If there were blood in the stools, the chances would be very greatly in favor of a spindle-cell tumor.

Occasionally, a small duct emptying into the lumen of the involved viscus has been described grossly on the pathological specimen of the aberrant pancreas. This was mentioned in a few of Branch and Gross's 24 cases. Kjellman[8,9] has described 6 cases in which he believes that the ducts were visualized radiographically when the barium entered them. Most of his illustrations are convincing. In 4 of his cases the aberrant nodule was in the duodenal bulb. Unfortunately, only 1 of his cases was confirmed pathologically, but he did have follow-up gastrointestinal studies several years apart in other cases that revealed no great change in the appearance of the lesions, the ducts being visualized on both occasions.

It is problematical whether the stellate shadow represented ducts within the lesion or wrinkles on the outer surface, but it was constant, so that I think it was a part of the lesion rather than on the opposite wall of the duodenal bulb. To decide whether those were ducts or not, we should like to see a profile view. A duct system opening into a lumen would present a more distinctive pattern in that view.

To arrive at a single diagnosis in the case under discussion, I shall have to make a number of assumptions: that the mass in the bulb was responsible for most or all of the symptoms and had therefore been present for at least twenty-two years; secondly, that, from its radiologic appearance, it arose in the mucosa or the submucosa; and, thirdly, that the stellate shadows were caused either by wrinkles on the surface or by ducts within the lesion. These assumptions would make the spindle-cell tumors rather unlikely since the overlying mucosa should be smooth and in the majority of cases the tumors lie deeper within the wall than this seemed to lie. The duration would fit a lesion such as aberrant pancreas, which is presumably present at birth and grows very slowly if at all. I do not believe, however, that the long duration entirely rules out an adenomatous polyp or a spindle-cell tumor, because they have been described as showing no change in size over a period of several years. The final and most convincing reason I have for thinking that this was an aberrant pancreas is that a small benign polyp would be a rather humdrum lesion to present at one of these sessions! I believe that this was an aberrant pancreatic nodule with a duct system visualized by barium, but I shall not be surprised if it turns out to have been an ordinary polyp.

DR. BENJAMIN CASTLEMAN: Dr. Ellis, you took care of this patient. Do you have any comment?

DR. DANIEL S. ELLIS: I have no clear conception about why the patient had pain all these years if he did not have an ulcerating lesion. I wonder if Dr. Tomchik has any explanation of pain on the basis of an aberrant pancreas?

DR. TOMCHIK: The lesion, although it was not actually pedunculated, probably moved around somewhat, exerting traction on the wall, and possibly caused pain in that way.

DR. ELLIS: I thought that the patient had an ulcerating lesion and that the surgical treatment should be that for an ulcer, at the same time that the tumor was removed.

A PHYSICIAN: Was there any blood in the stool?

DR. MARSHALL K. BARTLETT: No.

When we explored the duodenum there was a sessile polypoid lesion attached to the anterior inferior wall just beyond the pylorus. It was quite soft but was easily felt. There was no scarring of the duodenum. We could not confirm the fact that a duodenal ulcer had been present in addition to the other lesion. However, because of the long story suggestive of ulcer, it seemed wise to do a procedure that would protect the patient from future ulceration so we did the usual type of subtotal resection of the stomach, including a portion of the duodenum to a point beyond the polypoid lesion. Our preoperative diagnosis was polyp of the duodenum.

CLINICAL DIAGNOSIS

Polyp of duodenum.

DR. FREDERICK S. TOMCHIK'S DIAGNOSIS

Aberrant pancreas of duodenum.

ANATOMICAL DIAGNOSIS

Aberrant pancreas of duodenum.

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: The pyloric polypoid mass was about 1.7 cm. in its greatest diameter; it was submucosal, and the mucosa over it moved freely. We were unable to find any ulceration over the lesion or anywhere else in the stomach. The duodenum and mucosa over the lesion were normal. It was aberrant pancreas in which were pancreatic ducts and acinar tissue in among the muscle tissue.

I do not know how to account for the symptoms. Has the patient been free of symptoms since the resection?

DR. ELLIS: Yes.

DR. CASTLEMAN: Perhaps, as Dr. Tomchik suggested, the lesion was so freely movable that it prolapsed on occasions, with pain as a result.

DR. BARTLETT: These lesions are said to imitate the pattern of ulcer symptoms, but I do not know any satisfactory explanation for that.

DR. ELLIS: As I looked at the specimen when it was removed, I should not have thought it was mobile enough to prolapse. This patient had an intermittent history that was perfectly consistent with the history of peptic ulcer.

DR. CASTLEMAN: How long has it been since operation?

DR. BARTLETT: I think that it is nearly two months. So far the symptoms have not recurred.

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A SLIDING SCALE FOR SOCIAL SECURITY

SOCIAL security, so-called, for the professional man and especially for the physician represents an economic dilemma. Not only does the doctor usually retire relatively late in life, if at all, thus having a diminished number of years in which to reap the benefits of participation, but he has no employer to share his payments into the pool. The physician consequently believes, not unjustly, that were he to be forced into participation in the plan he would be doubly taxed and meagerly rewarded.

Senator Paul Douglas, of Illinois, early this year introduced an element of flexibility into the rigid social-security structure by proposing amendments to the new social-security bill that would allow participants to start collecting benefits as early as age sixty, at a lowered rate, or to delay accepting them to as late as age seventy-two, when the annual returns would be higher than at par. According to the Douglas plan the participant retiring at age sixty would receive 80 per cent of the standard benefits, 4 per cent being added for each year of continued employment. At age sixty-five 100 per cent of standard would be reached, after which benefits would begin to increase to age seventy-two and beyond, when the payments would be 128 per cent of parity.

Such a modification would seem to make participation more tolerable for the self-employed physician who does not wish to retire at sixty-five or cannot afford that luxury; however, the plans evolved by Dr. Harold Swanberg, editor of the *Mississippi Valley Medical Journal* and secretary of the American Medical Writers' Association, as published in the May, 1956, issue of that journal, more than doubles the inducement to participate by providing an almost lavish incentive to remain at work.

According to the Swanberg plans 8 per cent would be subtracted from the benefits for each year of retirement below the age of sixty-five, beginning at age sixty, and either 8 or 12 per cent would be added for each year of work beyond the somewhat arbitrary but widely accepted standard age of sixty-five for retirement. Thus, according to the 8 and 12 per cent plan, those retiring at sixty would receive 60 per cent of the standard benefits per annum, whereas those continuing to cultivate the vineyard until the Biblical threescore years and ten (plus two) had been reached would be rewarded for their prolonged industry by then receiving 156 per cent of the normal benefits.

Under both the Swanberg and Douglas plans, as at present, the participant who had attained these ripe years could continue at full earning capacity, or resume it, freed from jeopardy. The destinies that shape men's ends would have given up their efforts to force him into retirement in order that he might collect his benefits, and would allow him to continue happily in full employment to the end of time, eating his cake as well as having it, or vice versa.

Social security having arrived, it is said, not soon to depart, the doctor might as well share in its benefits, but on terms adapted to his particular economic situation.

"VANITY AND VEXATION"

PROBABLY most physicians who began the practice of medicine a generation or more ago are still sure that it is best practiced by individuals. However, the conditions of practice change, problems arise that were unknown thirty or forty years ago, and scientific, social and economic principles then valid are no longer clearly applicable or completely adequate.

In Massachusetts a further handicap exists because there is no legal definition of what constitutes the practice of medicine. Chapter 176C of the *General Laws* of the Commonwealth (*Acts* of 1941, Chapter 334) provides that a medical-service corporation is exempt from the provisions of Chapter 112 (relating to the practice of medicine), and specifically states that such corporations shall *not* be deemed to be practicing medicine. Yet they may hire physicians to practice in their behalf. (It is hard to see how a corporation could practice medicine in any other way than by hiring physicians.)

For many years the charitable Boston Dispensary hired physicians to visit the sick poor. No financial profit was involved, since the only money received by the Dispensary was from its philanthropic supporters, and the patients were unable to contribute anything.

But when a new day dawned and the sick poor, if willing to "go on relief," were provided with medical care paid for out of tax monies, neither the Dispensary and other incorporated hospitals nor many private physicians were sufficiently independent financially to turn down fees offered in behalf of welfare patients.

The questions have been raised repeatedly whether it is proper for such a hospital or physician to charge fees comparable to those received in private practice, and whether a corporation that hires physicians should accept fees and pay salaries to the physicians, retaining for its own benefit the excess received from patients above the salaries paid.

The problem is complicated by the questions whether a hospital is practicing medicine if it charges patients for x-ray studies, anesthesia or psychiatric examinations, and pays the physician who is actually responsible for the work less than the fee collected, and whether insurance companies or medical-service organizations like Blue Shield should make payments to a hospital that employs resident physicians, or should be required to pay resident physicians directly for services rendered to their subscribers.

These and many other questions have vexed the profession for a number of years. Relief is to be sought first by efforts to ensure that the laws, while protecting the individual who practices independently, are flexible enough to permit large teaching hospitals and service organizations to function adequately; secondly, by continued study of these matters by medical societies and individual physicians; and thirdly, by mutual agreement between organizations representing the physician and those representing corporations that engage in medical practice. All, of course, should be consistent with accepted principles of medical ethics.

One may still occasionally be reminded of the lines of George Crabbe, penned some hundred and fifty years ago and probably little known in these more realistic days:

> Oh, rather give me commentators plain,
> Who with no deep researches vex the brain;
> Who from the dark and doubtful love to run,
> And hold their glimmering tapers to the sun.

MY SISTER'S KEEPER

THERE is never a time when friendship is not among the most valued contributions that life has to offer, and never, in a perennially confused society, has the co-operative understanding that friendship engenders been more necessary than in the restless present. The grim results of its absence have been repeatedly demonstrated on a major scale, and its influence on the life of the individual is a matter of common experience.

Social agencies, with their organized efforts, can hardly duplicate the spontaneous relations that arise between individuals, but certain ones, in their way, can be responsible for excellent substitutions that might not otherwise be obtainable. Six years ago the Big Sister Association of Greater Boston was established by a few discerning women of Boston and Cambridge for the one purpose of bringing the protective influence of friendship to girls in special need. The belief was that it is simpler to prevent at their beginning than to try and solve later the various problems that life sometimes presents to these young women. The Association was incorporated in the following year and, under the active presidency of Mrs. Frank H. Pardee, has been continually expanding its program.

Big sisters, in the meaning of their Association, are women interested in the welfare of girls from all economic and social stratums, regardless of race or creed, "who need understanding friendship, counsel and skillful guidance, for the purpose of preventing delinquency" and the fostering of such growth in the individual as will sustain her in the future. The relation consists of a friendly and protective bond between a mature and well adjusted adult and a girl in need of such adjustment.

Little sisters are referred to the Association by clinics, schools, settlement houses and individuals;

big sisters are enlisted by going out into the fields and vineyards and finding those who have compassion, an abundance of friendliness and a desire to be of service. As the offer of Knowledge, in the mystery play, might be paraphrased: "Everywoman, I will be thy guide, in thy most need to go by thy side."

JEWISH MEMORIAL HOSPITAL BULLETIN

WITH the publication of Number 1, Volume 1, of the *Jewish Memorial Hospital Bulletin* in October, 1955, the fiftieth anniversary of the establishment of the hospital itself was also celebrated. The fact that the present acknowledgment of the first appearance of a very young periodical and of the semicentennial celebration of a not-so-young institution is made some little time after the appearance of the second issue of the semiannual bulletin is neither here nor there. The world is too much with us and always has been.

The important point is that for over six months the determination to compose a greeting to the *Jewish Memorial Hospital Bulletin* and a felicitation to the Hospital itself has not weakened or been forgotten but has strengthened with each parting month. This greeting to the *Bulletin* and to the hospital of its origin is the result, therefore, of no idle impulse but is a deliberate, seemly, sincere and long-contemplated tribute, which did not need the reminder that the receipt of the April issue brought, although that, too, had its activating influence.

The contents of the two bulletins so far published consist of the reports of investigations and observations made in the hospital wards and laboratories and are of the high grade that might be expected. The clinicopathological conferences are ably presented by Dr. Alfred Schwarz, who is also to be congratulated for his literary workmanship as editor-in-chief of the *Bulletin*.

With this number, the fifty-fifth volume of the Journal begins. It is our constant endeavor to improve, so far as in us lies, the character of this long-established periodical. We can, with truth, announce it to be in a flourishing condition, and there is much to encourage us with regard to its future prospects.

Boston M. & S. J. *August 7, 1856*

MASSACHUSETTS MEDICAL SOCIETY

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BENZENE HAZARDS

Many persons are unaware that benzene, a colorless, volatile liquid, still extensively used as a cleaner, solvent and thinner, and found in many paint and varnish removers and in certain rubber cements, is a *highly toxic* chemical, being the most toxic of all the known solvents. Sometimes preferred because it is relatively inexpensive as well as being effective for these purposes, it can be quickly absorbed into the system of the user, both by the skin and by inhalation. It then depresses the bone marrow, where blood cells are formed, leading to fatal aplastic anemia. Continued exposure to small amounts can lead to chronic anemia and also to chronic liver damage.

Benzene (not to be confused with benzine, which denotes gasoline or kerosene) is still employed commercially, in addition to the uses mentioned above, as a thinner in natural and artificial rubber and in artificial-leather dopes, and also as a beginning chemical in many industries.

Although the dangers of use of benzene have been recognized by federal and local governmental agencies, and a special law in Massachusetts requires that all receptacles containing this chemical must be labeled in a unique manner, there are a good many states where one can purchase paint removers that have not been carefully labeled, with the result that present-day exposure to benzene is more frequent than might be expected.

Failure on the part of the unsuspecting patient to mention his exposures to such toxic chemicals, as well as failure on the part of the physician to inquire about the possibility of such exposures, has caused the death of the patient in many cases.

GEORGE F. MORRIS, M.D.

*George F. Wilkins, M.D., *chairman;* Henry C. Marble, M.D.; Karl T. Benedict, M.D.; Harriet L. Hardy, M.D.; George E. Morris, M.D.; Albert O. Seeler, M.D.; and Jermyn F. McCahan, M.D.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

COMMUNICABLE DISEASES IN MASSACHUSETTS FOR JUNE, 1956

RÉSUMÉ

DISEASE	JUNE 1956	JUNE 1955	SEVEN-YEAR MEDIAN
Chancroid	1	3	4
Chicken pox	1737	1870	1410
Brucellosis	1	2	2

Diphtheria	0	0	3
Dog bite	1890	1789	1657
Dysentery, bacillary	1	5	5
Encephalitis, infectious	0	2	4
German measles	1189	397	665
Gonorrhea	149	171	177
Granuloma inguinale	0	0	0
Hepatitis, infectious	31	74	13
Lymphogranuloma venereum	2	1	1
Malaria	0	0	1
Measles	412	1706	2556
Meningitis, meningococcal	2	4	6
Meningitis, Pfeiffer bacillus	4	1	4
Meningitis, pneumococcal	0	0	3
Meningitis, staphylococcal	0	0	0
Meningitis, streptococcal	0	0	0
Meningitis, undetermined	4	4	4
Mumps	473	851	1004
Poliomyelitis	3	8	6
Salmonellosis	46	35	9
Scarlet fever	475	692	364
Syphilis	175	150	154
Trichinosis	0	2	2
Tuberculosis, pulmonary	186	146	179
Tuberculosis, other forms	4	11	11
Typhoid fever	2	1	2
Whooping cough	44	116	141

Comment

Diseases below the seven-year median were diphtheria, bacillary dysentery, measles, mumps, poliomyelitis and whooping cough.

No cases of diphtheria were reported during the month of June. The total number of cases of this disease reported during the six months beginning January 1 was only 6 — a record low for this period.

Only 1 case of bacillary dysentery was reported during the month of June. The total for the six-month period is 6 — the lowest figure for this period since 1933.

Only 44 cases of whooping cough were reported during the month of June. This is less than half of the previous low for this month.

Diseases above the seven-year median were chicken pox, German measles, infectious hepatitis, salmonellosis and scarlet fever.

Salmonellosis continues at a high level. Sporadic cases are the rule and are reported with equal frequency from all parts of the State.

Geographic Distribution of Certain Diseases

The following diseases were reported from the communities named:

Brucellosis: Framingham, 1.

Diphtheria: Newton, 1.

Dysentery, bacillary: Everett, 1.

Hepatitis, infectious: Amherst, 1; Attleboro, 1; Boston, 6; Brockton, 1; Cambridge, 1; Chelsea Naval Hospital, 2; East Longmeadow, 1; Fall River, 1; Fitchburg, 1; Framingham, 1; Holyoke, 2; Ludlow, 1; Needham, 2; Newton, 1; Seekonk, 1; Somerville, 1; Waltham, 1; Wellesley, 2; Wilbraham, 1; West Bridgewater, 1; West Springfield, 1; Westwood, 1; total, 31.

Meningitis, meningococcal: Tyngsborough, 1; Wilbraham, 1; total, 2.

Meningitis, Pfeiffer bacillus: Fall River, 1; Huntington, 1; New Bedford, 1; Springfield, 1; total, 4.

Meningitis, *Escherichia coli*: Belchertown, 1.

Meningitis, mumps: Cambridge, 1; Framingham, 1; Marlboro, 1; Watertown, 1; total, 4.

Meningitis, undetermined: Belmont, 1; Haverhill, 1; South Hadley, 1; West Springfield, 1; total, 4.

Meningococcemia: Belchertown, 1; Lowell, 1; total, 2.

Poliomyelitis: Framingham, 3.

Psittacosis: West Bridgewater, 1.

Rocky Mountain spotted fever: Waltham, 1.

Salmonellosis: Boston, 5; Cambridge, 1; Chicopee, 1; Framingham, 2; Holyoke, 1; Lawrence, 1; Lexington, 1; Lowell, 4; Melrose, 2; Natick, 1; Needham, 2; Newton, 3; North Adams, 1; North Reading, 1; Northampton, 1; Peabody, 1; Quincy, 1; Springfield, 7; Swampscott, 1; Watertown, 3; Wellesley, 1; Wenham, 1; West Boylston, 1; West Bridgewater, 1; Weymouth, 1; Worcester, 1; total, 46.

Typhoid fever: North Adams, 1; Southbridge, 1; total, 2.

CORRESPONDENCE

CALIFORNIA CONTROVERTS

To the Editor: We should like to call attention to several errors in the article entitled "A Statistical Appraisal of the Protein-Bound Iodine as a Test of Thyroid Function," by M. E. Dailey and J. R. Skahen, which appeared in the May 10 issue of the *Journal*. This article states, among other things, that there was no significant difference in PBI between hypothyroid and euthyroid patients, but this conclusion is not supported by the data cited, probably because of errors in computation, formulation and statistical reasoning.

Regarding errors of computation, we note the following discrepancy. In the euthyroid control group (1) there are 250 women and 63 men, the means and standard deviations for these two groups being shown in Figure 1 as 6.19 ± 1.09 and 6.16 ± 0.92, respectively. In Figure 2 the euthyroid control group is shown to have 313 cases, in agreement with the data of Figure 1, but here the mean is given as 6.16 and the standard deviation as 1.49. It is a simple matter to recalculate from the male and female groups of Figure 1 what the values should be in Figure 2: these come out as 6.18 ± 1.06. The data shown in Figures 1 and 2 are therefore incompatible, most probably because of computational error. Although the magnitude of the errors here noted would probably not greatly affect conclusions drawn from the data, such errors do not encourage confidence in a work intended to be a statistical appraisal.

The authors appear, however, to have made much more drastic errors in their calculation of t and p values, upon which they rest their conclusions. The standard deviations cited above are clearly the measurement of variation of individuals composing the samples, since the mean plus and minus 1 6 includes about two thirds of the cases. The simplest and most widely used test of the significance of the difference between two means — and this test is entirely applicable here — is to find

$$t = (\bar{x}_1 - \bar{x}_2) / \sqrt{V\bar{x}_1 + V\bar{x}_2} ,$$

where $\bar{x}_1$ and $\bar{x}_2$ are the two means and $V\bar{x}_1$ and $V\bar{x}_2$ are the variances of the means. The variance of the mean, of course, is found by dividing the variance (σ^2) of the individuals composing the sample by the number of individuals. Using the statistics presented in Figure 2 for the euthyroid group, we have found the variance of the mean to be 0.00709. Similarly, the variance of the mean of the clinically hypothyroid group is 0.01921. The standard error of the difference between the means of these two samples is therefore

$$\sqrt{0.00709 + 0.01921} ,$$

or 0.162. The means of the two groups (as given in Figure 2) are 6.16 for the euthyroid and 3.58 for the hypothyroid group. The difference between means is 2.58, and this divided by 0.162 yields a t value of 15.9, which is indeed enormous. The p value corresponding to this is infinitesimal, as may be judged from the fact that a t of about 2 carries a p value of 0.05, whereas a t of only 3.3 carries a p value of 0.001. Only use of the wrong formula can account for the statement in the article that this difference in means carries a t of 1.11 (rather than 15.9) and is therefore not significant. It appears that, among other things, the authors may have failed to recognize the difference between the standard deviation of individuals and the standard deviation of the mean. In any event, the data published demonstrate beyond doubt that the PBI is low in hypothyroid patients and the authors have erroneously and misleadingly concluded that that is not so.

One further misleading statement appears concerning Figure 2. This deals with the extent of "overlap" between the euthyroid and hypothyroid values. It is stated that "The levels in the top 25 per cent of the hypothyroid group were equal to those in the lowest 25 per cent of the euthyroid group." Here, the authors missed an opportunity to point out that the normal sigmoid curve theoretically does not reach either 0 or 100 per cent but merely becomes asymptotic with these limits. In an abstruse way, therefore, the hypothyroid curve reaches out through a series of infinitesimal probabilities to cover the entire euthyroid range, and

vice versa, so that the overlap could be said to be 100 per cent of each curve over the other. The analysis made by the authors is as meaningless as this proffered caricature. The point of real importance is this: careful inspection of the two curves discloses that the point of equivalence is about 6 per cent — that is, one finds that there are about 6 per cent of the hypothyroid persons with PBI greater than about 4.2 gamma while a similar percentage of euthyroid patients had a PBI of less than 4.2 gamma. Stated another way, this means that 94 per cent of the hypothyroids had PBI levels lower than those found in 94 per cent of the euthyroid cases. The clinical value of a test that makes such a massive distinction must be perfectly apparent, but this is directly opposite to the view expressed in the article, in which the authors conclude that it "is of little value in the diagnosis of hypothyroidism."

It is to be regretted that publication of such an article, the conclusions of which are erroneously derived, should bear weight against a test of proved clinical value. Aside from the completely fallacious conclusions reached, perhaps a greater tragedy lies in the fact that it is through just such incidents that the value of statistics has become suspect by many members of the medical profession.

RICHARD J. HENRY, M.D.
Assistant Clinical Professor of Medicine
PAUL STARR, M.D.
Professor of Medicine
FREDERICK J. MOORE, M.D.
Professor of Experimental Medicine
School of Medicine, University of Southern California
Los Angeles

This letter was submitted to Drs. Dailey and Skahen, who offer the following reply:

To the Editor: Regarding the letter of Drs. Henry, Starr and Moore we wish to make the following brief comment.

In reviewing the data in the light of the letter from Dr. Starr et al., it is found that an error was indeed made in computing the variance of the means between the hypothyroid and the euthyroid groups. There is a difference between these two groups, and the difference is of unquestionable statistical significance.

The question of its practical significance is answered in part by the writers of the letter — that is, one can choose a cut-off value — near 4 gamma per 100 ml. — such that about 6 per cent of the euthyroid patients fall below it and about 6 per cent of the hypothyroid patients fall above it; the test has rather good discriminatory power in this regard.

Another aspect of practical import that was raised in the original paper is that values as low as 4 gamma per 100 ml. ordinarily are associated with clinically obvious hypothyroidism, in which case little information is added by the PBI value.

MORRIS E. DAILEY, M.D.
J. RICHARD SKAHEN, M.D.
San Jose, California

UNQUOTE

To the Editor: Many laymen are understandably confused and amazed by some of the public statements of various physicians about President Eisenhower. Is it not time for us in the profession to admit freely that the information given out concerning the President's illness has often been incomplete and misleading?

The statements that disturb our lay friends — and should distress us even more—range all the way from Dr. White's remark that the President "should be able to carry on an active life for another five to ten years," this without qualification except for the phrase "fully aware of the hazards and uncertainties that lie ahead," and his subsequent pronouncement that the President was a completely normal person before his heart attack, through the recent depositions from the Walter Reed Hospital that the President is "better than ever" since his operation, to the astonishing remark credited by at least two newspaper columnists to Dr. David Allman, president-elect of the American Medical Association, that "when Mr. Eisenhower recovers he will be in better physical condition than any of his opponents, Republican or Democrat, have been at any time in their lives."

It is conceivable, though unlikely, that some of these physicians have been misquoted by the press. If so, it is not only their privilege but their duty to correct publicly any such misquotation.

It is, of course, absurd for any doctor to say that he can give no opinion "because he has not seen the case." Assuming that we are correctly informed and that the President has had a coronary occlusion and now has regional ileitis sufficiently active to cause obstruction, it is inconceivable that any individual case could present physical findings or other evidence that would justify any such rosy predictions as have emanated from Washington. A large body of literature indicates that prognosis in both conditions must be most cautious and uncertain.

One wonders if members of the medical profession have on any other occasion dished out such a combination of misinformation and silly remarks. Is it too much to expect some judicious balance, at least an approach to scientific objectivity, from our colleagues in their public statements, especially when they are dealing with a situation loaded with so much importance to the country and the world? Are we to leave it to newspapers like the *Milwaukee Journal* and columnists like Doris Fleeson and James Reston to point to the degrading effect on our profession of such public utterances?

PHILIP M. LECOMPTE, M.D.
Newton Center, Massachusetts

BOOK REVIEWS

Pathology Seminars. By Lauren V. Ackerman, M.D.; Arthur C. Allen, M.D.; J. E. Ash, M.D.; Arthur Purdy Stout, M.D.; and Rupert A. Willis, M.D. Edited by Robert S. Haukohl, M.S., M.D., and W. A. D. Anderson, M.D. 4°, cloth, 195 pp., with 131 illustrations. St. Louis: The C. V. Mosby Company, 1955. $10.00.

A "slide seminar" has become a popular educational exercise for conferences of pathologists. These usually consist of a discussion, led by a guest pathologist, of a group of diagnostic problem cases on which appropriate clinical data and microscopical slides have been previously distributed to all participants. This is a small book containing the edited transcription of five such seminars, including comments and questions, with the listed authors acting as the individual discussers.

The discussers are well known pathologists and acknowledged authorities in special fields, and many of the cases have been selected on the basis of their relation to the discusser's particular interests. As is usual with such seminars, the majority deal with tumors, and four of the five in this volume are made up of such cases. A total of 51 cases of tumor are individually discussed in the book, and many of these are of the unusual or rare variety.

The seminars conducted by Drs. Ackerman, Stout and Willis cover a wide range of interesting neoplasms, frequently of a controversial nature. The seminar by Dr. Ash is devoted to a group of tumors of the nose and throat, which he selected to represent clinical entities rather than problems in diagnosis. Dr. Allen contributes a section, entitled "An Introduction to the Pathology of the Skin," that departs from the presentation of specific clinical cases and emphasizes classification and illustration of many dermatoses.

One attraction of the seminar technic is its adaptation to informal expressions of opinion as stimulated by open-forum discussions of problem case material. An inherent drawback to publishing the transactions of such exercises is the reader's dependence on photomicrographs (which are of good quality) for his diagnostic impression of selected difficult cases, whereas the discussion text was originally directed to an audience that had had opportunity to study the microscopical slides individually. However, many personal views and sidelights of the discussers scattered through the book are interesting from both factual and philosophic

standpoints, making for pleasant and informative reading. Owing to its specialized contents this type of book has an appeal principally to pathologists and in particular to surgical pathologists. The clinical data accompanying the cases are in brief abstract form; x-ray films are not included.

AUSTIN L. VICKERY, M.D.

Antimicrobial Therapy in Medical Practice. By Harrison F. Flippin, M.D.; and George M. Eisenberg, D.Sc. 8°, cloth, 284 pp., with 11 tables. Philadelphia: F. A. Davis Company, 1955. $5.00.

This is a timely volume by authors with extensive experience in the field, one in the clinic and the other in the laboratory. The book offers practical presentations directed at the practitioner and offering primarily the point of view of the authors. A list of references to each chapter, arranged alphabetically by authors, is appended at the end of the book; these include a disproportionate number of titles by the authors and their associates but only a random selection by others. A foreword by Dr. Richard A. Kern expresses very well the growing concern about the great abuses of antibiotics and about their untoward consequences.

MAXWELL FINLAND, M.D.

Grosse Nervenärzte. Edited by Prof. Dr. Kurt Kolle, München. 8°, cloth, 284 pp., with 21 illustrations. Stuttgart: Georg Thieme, 1956. DM 29.40.- $7.00. (Distributed in the United States by Intercontinental Medical Book Corporation, New York City.)

The lives of 21 neurologists, neurosurgeons, physiologists and psychiatrists have been carefully evaluated by competent scholars in this multiple-author book, edited by Dr. Kurt Kolle, of München. The biographies, with portraits, are comprehensive and give a clear picture of each man, his place in medicine and his influence on the progress in knowledge of the workings of the nervous system and the diseases particularly associated with it. Few will adversely criticize the selection of the men to be honored and those chosen to write about them. Berger, Cajal, Charcot, Cushing, Erb, Freud, Hughlings Jackson, Moniz, Pawlow, Pinel and Sherrington could hardly be left off any list. Bleuler, Bonhoeffer, Foerster, Griesinger, von Gudden, Jaspers, Jung, Kraepelin, Rieger and von Jauregg might not receive quite such universal accord, and yet it is the biographies of this second list that give the book a particular distinction, for facts about them are difficult to find, particularly for English-speaking readers. Dr. John F. Fulton has done well with Cushing and Sherrington, Minkowski with Pawlow, Gordon Holmes with Jackson, Nonne with Erb, and Kolle with Berger, as might be expected. Notes on Swiss and German clinics and professors are appended in tables, but the book lacks an index. Bibliographic references are added, and the monograph is finely printed and illustrated. As a sound reference book, this biographic analysis can be fully recommended.

HENRY R. VIETS, M.D.

Psychoanalysis and Psychotherapy: Developments in theory, technique, and training. By Franz Alexander, M.D. 8°, cloth, 299 pp. New York: W. W. Norton and Company, Incorporated, 1956. $4.75.

This book is a scholarly and honest attempt to put emphasis on a most important subject: psychotherapy in the general field of psychoanalysis. It has long been known that psychoanalysis per se is not necessarily psychotherapeutic. Some analysts are good analysts, and some are good therapists. The psychoanalyst with psychotherapeutic ability is a doubly gifted man. Franz Alexander, M.D., is one of these rare persons, pre-eminently a psychoanalyst from his early training in Austria-Hungary. He has always remained a physician, and in the last twenty-five years he has demonstrated his powers of leadership as director of the Chicago Institution for Psychoanalysis, at the same time building for that institution a unique reputation of value as a force in the country and a good-will agent. Among strictly orthodox psychoanalysts he has always been somewhat of a liberal, — at times (when pioneering) even something of a nonconformist, — but his ends have justified his means, for now he has come to that summit "—where the eye sees the world as one vast plain and one boundless reach of sky." From such a vantage point he has written this delightful book. It is readable and informative and at the same time faces facts in a way one might wish more of his colleagues could attain.

The book is broadly based from a lifetime of experience and many years of intensive study. Dr. Alexander defines the position of psychoanalysis in Western culture and points out the ways in which the theory of psychoanalysis can be co-ordinated with the elemental facts of treatment. His unique experience qualifies him especially well to discuss the modification in the technic of psychoanalysis as first stated by Freud. He ponders the ideas of flexibility and what he calls "corrected emotional experience." He does not omit mention of the important aspects of treatment with technical "transference" (feelings of the patient toward the therapist) and "countertransference" (feelings of the therapist toward the patient). He emphasizes controversial issues in a constructive, forward-looking way, and he closes his volume with some well stated and very important ideas about the teaching of psychoanalysis, including the opinions of eminent contemporary teachers in psychiatry.

This is an inspiring and stimulating book. The printing is excellent. The author honors Freud by dedicating this book to the founder of psychoanalysis on the hundredth anniversary of his birth.

MERRILL MOORE, M.D.

NONCLINICAL NOTES

AMERICAN NEUROLOGICAL ASSOCIATION

At the eighty-first annual meeting of the American Neurological Association the following officers were elected for the year 1956-57: Dr. H. Houston Merritt, president; Dr. Israel S. Wechsler, president-elect; Dr. Richard B. Richter, first vice-president; Dr. Augustus Rose, vice-president; Dr. Charles Rupp, secretary-treasurer; and Dr. William F. Caveness, assistant secretary.

NOTICES

ANNOUNCEMENT

Dr. James Davis Allan announces his association with the Douglas Clinic, Westfield, Massachusetts, in the practice of general surgery.

NATIONAL HEMOPHILIA FOUNDATION

The Medical Advisory Council of the National Hemophilia Foundation will hold an International Symposium on Hemophilia at the Ambassador Hotel, Park Avenue at 51st Street, New York City, on August 24 and 25.

Further information may be obtained from Dr. Martin C. Rosenthal, National Hemophilia Foundation, 175 Fifth Avenue, New York 10, New York.

THE MEDICAL ASSOCIATION FOR THE PREVENTION OF WAR

The Medical Association for the Prevention of War is offering a prize of £75 ($210.00), to be called the John Ryle Memorial Prize, for the best essay under the title "A World Approach to Human Survival and Health." This prize is open to qualified medical practitioners and students of any nationality. Further information may be obtained from Dr. D. L. Kerr, Hon. Secretary, Medical Association for the Prevention of War, 291 Burntwood Lane, London, S.W. 17.

AMERICAN UROLOGICAL ASSOCIATION

The American Urological Association announces the annual urology award of $1,000 (first prize, $500, second prize, $300, and third prize, $200) for essays on the result of some clinical or laboratory research in urology.

Competition will be limited to urologists not more than ten years after graduation and to hospital interns and residents doing research work in urology. All essays must be submitted before December 1, 1956.

The first prize essay will be presented on the program of the next meeting of the American Urological Association, Hotel William Penn, Pittsburgh, Pennsylvania, May 6-9, 1957.

Further information may be obtained from William P. Didusch, Executive Secretary, American Urological Association, 1120 North Charles Street, Baltimore, Maryland.

SOCIETY MEETINGS AND CONFERENCES

AUGUST 3–AUGUST 28. Consultation Clinics for Crippled Children in Massachusetts. Page 1244, issue of June 28.
AUGUST 19–23. American College of Chest Physicians. Page 840, issue of November 10.
AUGUST 24 and 25. National Hemophilia Foundation. Page 249.
SEPTEMBER 3–5. Congress on Blood Transfusion, Blood Banks and Hematology. Page 297, issue of February 9.
SEPTEMBER 3–7. First Inter-American Conference on Occupational Medicine and Toxicology. Page 152, issue of July 19.
OCTOBER 8–13. International Cancer Cytology Congress. Page 104, issue of July 12.
OCTOBER 19 and DECEMBER 14, 1956, and FEBRUARY and APRIL, 1957. Massachusetts Society for Research in Psychiatry. Page 56, issue of July 5.
OCTOBER 30 and 31 and NOVEMBER 1. New England Postgraduate Assembly, Boston.

CALENDAR FOR THE WEEK BEGINNING THURSDAY, AUGUST 9

THURSDAY, AUGUST 9
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Surgical Grand Rounds. Dr. John Spellman and staff. Saint Elizabeth's Hospital.
*8:45–9:45 a.m. Cardiac Grand Rounds. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*9:00–10:00 a.m. Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.
*9:00–10:00 a.m. Arthritis Grand Rounds. Robert Breck Brigham Hospital.
*10:00–11:00 a.m. Combined Medical-Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–12:00 m. Medical Grand Rounds. Dr. Sylvester McGinn and staff. Saint Elizabeth's Hospital.
*11:00 a.m.–12:00 m. Medical Staff Conference. Sherman Auditorium, Beth Israel Hospital.
*11:00 a.m.–12:00 m. Pediatric Conference. Mount Auburn Hospital, Cambridge.
*11:00 a.m.–12:30 p.m. Hand Clinic (Physical Medicine and Rehabilitation Service). Boston City Hospital.
*12:00 m. Clinicopathological Conference. Dr. Benjamin Castleman and associates. Pathology Amphitheater, Massachusetts General Hospital.
*12:15–1:15 p.m. Tumor Clinic. Dr. T. W. Botsford. Amphitheater, Peter Bent Brigham Hospital.
*3:00 p.m. Thoracic Conference. The Circuit Presents Cases of Medical and Surgical Interest. Drs. Warren J. Taylor and Wendell B. Thrower. Main Amphitheater, Peter Bent Brigham Hospital.
5:00 p.m. Case Presentation and Pathological Discussion Followed by a Subject of Special Presentation. Joslin Auditorium, New England Deaconess Hospital.

FRIDAY, AUGUST 10
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*9:30–11:30 a.m. Medical and Surgical Grand Rounds. Drs. George W. Thorn and Francis D. Moore. Main Amphitheater, Peter Bent Brigham Hospital.
*10:00 a.m. Tuberculosis Surgical Clinic. South End Health Unit, 57 East Concord Street.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*12:00 m. Pediatric Grand Rounds. Thorndike Amphitheater, Boston City Hospital.
*1:30 p.m. Fertility and Endocrine Clinic. Free Hospital for Women, Brookline.
*1:30 p.m. Tumor Clinic. Mount Auburn Hospital, Cambridge.
*2:00–3:00 p.m. Pathology Conference. Dr. James Graham. Saint Elizabeth's Hospital.
*4:00–10:00 p.m. Alcoholism Clinic. By appointment. Washingtonian Hospital, 41 Morton Street, Jamaica Plain.
*4:30 p.m. Neuroradiologic Conference. X-Ray Conference Room, New England Deaconess Hospital.

SATURDAY, AUGUST 11
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:30–10:00 a.m. Orthopedic Staff Conference. Boston City Hospital.
*8:30–10:00 a.m. Surgical Grand Rounds. Dr. Charles G. Child, III, A. J. A. Campbell and staff. First (Tufts) Surgical Service, New Cheever Amphitheater, Dowling Building, Boston City Hospital.
*9:30–11:00 a.m. Surgical House Officers' Conference. Second-Floor Conference Room, Carney Hospital, Dorchester.
*10:30 a.m. Teaching Ward Rounds. Ward South 2, Free Hospital for Women.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

MONDAY, AUGUST 13
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:30–9:30 a.m. Clinic by Entire Surgical Staff and Anesthesia Staff. New Cheever Amphitheater, Dowling Building, Boston City Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–12:30 p.m. Staff Conference. Child Psychiatry. By appointment. Conference Room (Burnham 7), Massachusetts General Hospital.
*12:15–1:15 p.m. Clinicopathological Conference. Main Amphitheater, Peter Bent Brigham Hospital.
*1:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*2:00–3:00 p.m. X-Ray Conference. Dr. William Carey. Saint Elizabeth's Hospital.
*3:00–4:00 p.m. Neuroradiologic Conference. Dr. Bertram Selverstone. Stearns Auditorium, New England Center Hospital.
*4:00 p.m. Clinicopathological Conference. Pathology Conference Room, Beth Israel Hospital.
*4:00–5:30 p.m. Anesthesiology Conference. Surgical Conference Room, Peter Bent Brigham Hospital.
*5:00–6:30 p.m. Anesthesia Group of the Lahey Clinic. Joslin Auditorium, New England Deaconess Hospital.

TUESDAY, AUGUST 14
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Medical Grand Rounds. Pathology Conference Room, Carney Hospital, Dorchester.
*10:30 a.m. Medical Grand Rounds. Main Conference Room (Ground Floor), Lemuel Shattuck Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*12:00 m.–1:00 p.m. Pediatric Grand Rounds. Burnham Memorial Hospital for Children (Burnham 4), Massachusetts General Hospital.
*12:15–1:15 p.m. X-Ray Conference. Dr. Merrill Sosman. Main Amphitheater, Peter Bent Brigham Hospital.
12:30–1:30 p.m. Medical Journal Club. Joslin Clinic. (Cafeteria) New England Deaconess Hospital.
*2:00–3:00 p.m. Hematology Conference. Dr. Mario Stefanini. Saint Elizabeth's Hospital.
*4:00–5:30 p.m. Anesthesia Conference. Dr. Benjamin Etsten. Stearns Auditorium, New England Center Hospital.
*5:00 p.m. Surgical Journal Review. Mount Auburn Hospital, Cambridge.
*5:00–6:00 p.m. Service Meeting Followed by Clinical Conference (Medical, Surgical, Obstetric). Faulkner Hospital.

WEDNESDAY, AUGUST 15
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Medical and Surgical Clinic on Diabetic Problems. Peter Bent Brigham II, New England Deaconess Hospital.
*8:00–9:00 a.m. Surgical Grand Rounds. Auditorium, Carney Hospital, Dorchester.
*9:00–10:00 a.m. Surgical Grand Rounds. Massachusetts Memorial Hospitals.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m. Orthopedic Grand Rounds. Bigelow Amphitheater, White 3A, Massachusetts General Hospital.
*12:00 m.–1:00 p.m. Boston State Hospital Psychiatry Seminar. Reception Building Auditorium, 591 Morton Street, Dorchester.
*12:00 m.–1:00 p.m. Roentgen Diagnostic Conference. 5th-floor teaching unit, Beth Israel Hospital.
*12:00 m.–1:00 p.m. Pediatric Clinicopathologic Conference. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*12:15 p.m. Vascular Rounds. Drs. Edward A. Edwards and Chilton Crane. D-Main, Peter Bent Brigham Hospital.
*12:30 p.m. Weekly Pathological Meeting. Joslin Auditorium, New England Deaconess Hospital.
*12:30–1:30 p.m. Weekly Staff Review of Autopsies. Dr. William A. Meissner. Joslin Auditorium, New England Deaconess Hospital.
*1:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*1:00 p.m. Massachusetts General Hospital Hand Clinic. The Clinics of the Massachusetts General Hospital.
*2:00 p.m. Rectal Clinic. Peter Bent Brigham Hospital.
*2:00–3:00 p.m. Pediatric Conference for Practitioners. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*4:00–5:30 p.m. Fracture Lecture. Boston City Hospital.
*4:00–6:00 p.m. Overholt Thoracic Conference. Joslin Auditorium, New England Deaconess Hospital.
*6:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.

*Open to the medical profession.